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VOLUME 15 NUMBER 12

DECEMBER, 1955

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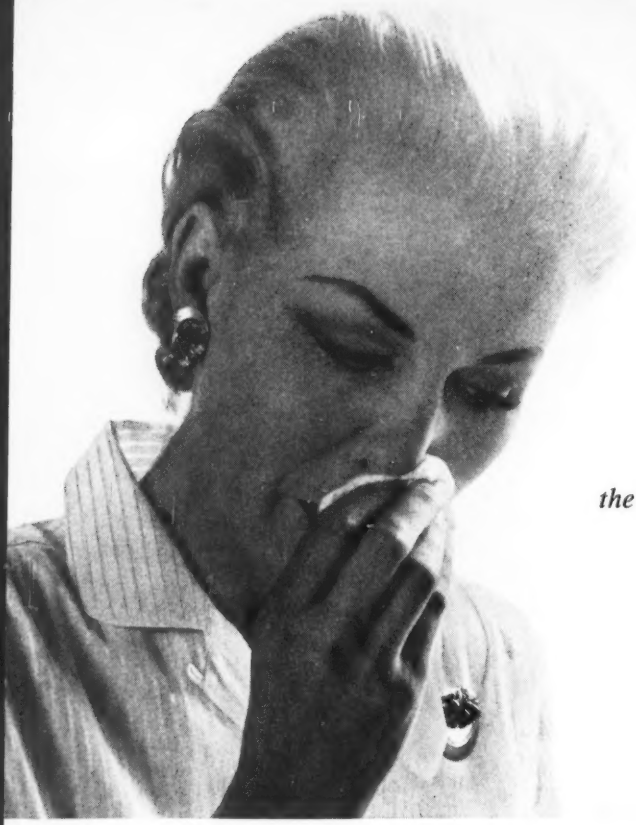

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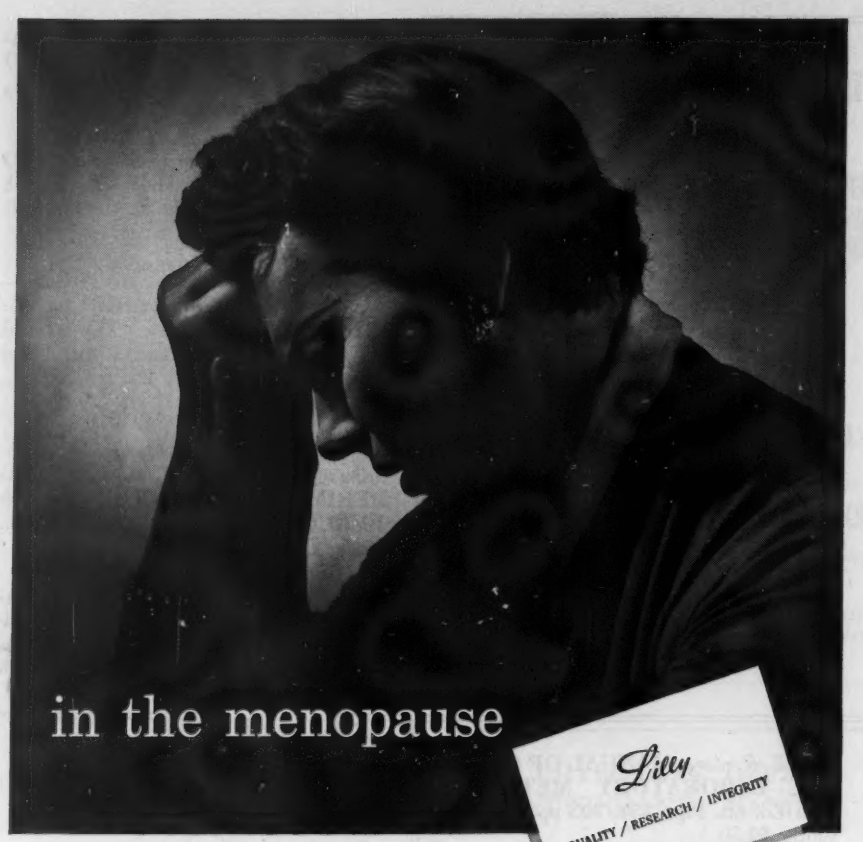

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VARIATIONS IN RENAL EXCRETION OF SODIUM INDEPENDENT OF CHANGE IN ADRENOCORTICAL HORMONE DOSAGE IN PATIENTS WITH ADDISON'S DISEASE*

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ALTHOUGH the important influence of the adrenal cortex upon renal conservation of sodium has been established for two decades (2–4), the precise role of adrenocortical hormones in the physiologic regulation of urinary sodium excretion remains poorly defined. It has been suggested that those alterations in renal sodium excretion which are dependent upon variation in renal tubular reabsorption are mediated, at least in part, by changes in adrenocortical activity. Inferential evidence that normal regulation of sodium excretion involves change in adrenal hormone activity (5, 6) has been strengthened by the reported observations of enhanced salt-

* A preliminary report (1) appeared as an abstract in the Proceedings of the Forty-Fourth Annual Meeting of the American Society for Clinical Investigation, Atlantic City, N. J., May 1950.

† Work done during tenure of a United States Public Health Service Post-doctorate Research Fellowship in Medicine, Thorndike Memorial Laboratory and Department of Medicine, Harvard Medical School. (Present address: Veterans Administration Hospital, Boston, Mass.)

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retaining activity in the urine of normal men maintained on salt-poor diets (7, 8).

The present communication describes experiments concerning the renal excretion of sodium by patients with Addison's disease who were receiving hormonal replacement therapy. It was argued that if such patients, while receiving a constant exogenous supply of adrenocortical hormones, manifested appropriate alterations in renal excretion of sodium when subjected to stimuli or circumstances known to produce such excretory changes in normal subjects, these changes could not reasonably be ascribed to alterations in the level of adrenocortical hormone activity. The observations to be described indicate that large and appropriate changes in sodium excretion independent of change in adrenocortical hormone level do indeed occur in such patients. This suggests that one role of the adrenal cortex in the regulation of sodium excretion is of the *permissive* type emphasized by Ingle (9, 10).

MATERIAL AND METHODS

The subjects were 2 men and 1 woman in whom the diagnosis of Addison's disease was well established. All 3 patients had exhibited classic manifestations of this disorder at some time before the present studies were carried out. Subjects C.K. and A.M. were hospitalized with impending Addisonian crisis: D.C., who had been receiving desoxycorticosterone for four years, was hospitalized during an acute hypoglycemic episode. Certain clinical data concerning the patients are presented in Table 1.

TABLE 1. CLINICAL DATA CONCERNING PATIENTS WITH ADDISON'S DISEASE

Subject	Age (yrs.)	Sex	Duration of symptoms* (months)	Blood pressure† (mm. Hg)	Pigmentation	Serum Na† mEq./L.	Serum K‡ mEq./L.	Urinary 17-keto-steroids, mg./24 hrs.	Eosinopenia after ACTH
C.K.	33	M	12	70/52	Vitiligo	110	6.3	1.8	None
D.C.	59	M	48	90/60	Moderate	141§	5.0§	—	—
A.M.	41	F	4	85/50	Marked	131§	5.2§	<2.0	None

* Prior to period of study.
† Lowest observed value.
‡ Highest observed value.
§ After DCA therapy indicated.

Each subject was studied both while receiving desoxycorticosterone acetate (DCA) alone and when cortisone was being given. The dosage schedules and dietary regimens employed at the time of each experiment are given in Table 2. Except when the diurnal variation of renal excretion was being studied, each experiment was conducted as follows. At approximately 8:30 A.M. (about one hour after breakfast) the subject voided, was weighed, and then over a period of thirty to sixty minutes ingested sufficient tap water to provide a load of 20 ml. per kilo of body weight.[1] The subject was weighed again and the water load maintained throughout the course of the experiment by oral administration

[1] In experiments M-2 and M-3 the water load was only approximately 10 ml. per kilo.

of enough water after each subsequent voiding to restore body weight to the level observed immediately after ingestion of the initial water load. In the experiments of group III, which involved the infusion of hypotonic saline solution several hours after water loading, the additional increment in weight observed after infusion was maintained for the remainder of the experiment. Timed voided urine collections were made at intervals of approximately thirty to sixty minutes (depending on rate of urine flow), usually beginning at the onset of water loading. Venous blood samples "arterialized" by

TABLE 2. THERAPEUTIC REGIMEN DURING EXPERIMENTAL PERIOD

Subject	Exp. No.	Study	Dietary sodium (mEq./day)	DCA	Cortisone
C.K.	K-1	Diurnal variation	224	1.25 mg., I.M. b.i.d.*	6.25 mg. P.O. b.i.d.
	K-2	Postural change	35	Pellets†	12.5 mg. P.O. b.i.d.
	K-3	Hypotonic infusion	150–250	Pellets	12.5 mg. P.O. b.i.d.
	K-4	Hypotonic infusion	35	Pellets	12.5 mg. P.O. b.i.d.
	K-5	Venous congestion	35	Pellets	12.5 mg. P.O. b.i.d.‡
	K-6	Postural change	150–250	Pellets	12.5 mg. P.O. b.i.d.
	K-7	Hypotonic infusion	150–250	Pellets	None
	K-8	Hypotonic infusion	150–250	Pellets	6.25 mg. P.O. b.i.d.‡
D.C.	C-1	Hypotonic infusion	ad lib.	2-mg. linguet t.i.d.§	None
	C-2	Hypotonic infusion	ad lib.	2-mg. linguet t.i.d.§	12.5 mg. I.M. b.i.d.
	C-3	Postural change	ad lib.	2-mg. linguet t.i.d.§	12.5 mg. I.M. b.i.d.
A.M.	M-1	Hypotonic infusion	ad lib.	2 mg. I.M. b.i.d.	None
	M-2	Postural change	ad lib.	2 mg. I.M. b.i.d.	None
	M-3	Postural change	ad lib.	1 mg. I.M. b.i.d.	12.5 mg. P.O. b.i.d.
	M-4	Hypotonic infusion	ad lib.	1 mg. I.M. b.i.d.	12.5 mg. P.O. b.i.d.

* B.i.d.—at 6 a.m. and 6 p.m.
† Pellets—5 DCA pellets, 125 mg. each.
‡ Morning dose of cortisone omitted.
§ Linguets omitted day of study; 3 mg. DCA in oil I.M. at 6 a.m.

heating the arm, were drawn about an hour after the water had been taken and thereafter at intervals designed to permit serial determinations of renal clearance of endogenous creatinine, sodium, chloride, and potassium. Serum total proteins (11), hemoglobin, and hematocrit were also measured. Further details of experimental technique and the analytical methods employed have been described previously (12, 13).

The percentage of filtered sodium excreted by the kidney ($E/F \times 100$) was estimated by means of the formula:

$$E/F = \frac{C_{Na}}{C_{Cr} \times 0.95}$$

in which C_{Na} is the renal sodium clearance and C_{Cr} the endogenous creatinine clearance, taken as a measure of glomerular filtration rate, and 0.95 is an assumed value for the Donnan equilibrium constant.

OBSERVATIONS AND INTERPRETATIONS

I. *Postural change*

The influence of change from the seated to the recumbent posture was observed four times in the 3 patients while both cortisone and DCA were

TABLE 3. RENAL EXCRETION OF WATER AND SOLUTES WITH CHANGE IN POSTURE

Subject and Exp. No.	Cortisone therapy (days)	Elapsed time* (min.)		Urine flow (ml./min.)		Na (μEq./min.)		K (μEq./min.)		Cl (μEq./min.)		Urine Na (mEq./L.)		Creat. clear. (ml./min.)		Sodium (E/F ×100)	
		S†	R‡	S	R	S	R	S	R	S	R	S	R	S	R	S	R
K-2	143	176–264	342–397	7.4	10.9	89	174	49	99	111	193	12	16	89	105	0.77	1.30
K-6	256	230–330	397–486	8.4	10.7	54	115	33	34	75	76	6	11	103	107	0.42	0.86
C-3	28	115–171	260–321	6.2	7.5	81	193	46	66	108	179	13	26	112	109	0.55	1.37
M-2	None	75–135	135–255	0.5	0.4	65	35	32	55	78	58	131	93	112	106	0.44	0.25
M-3	5	95–155	155–245§	2.7	2.1	199	205	68	88	65	87	74	99	81	78	1.90	2.01

* After water loading initiated.
† S—Last period seated prior to assuming recumbency.
‡ R—Period of maximal sodium excretion while recumbent.
§ Resumed sitting posture, 162–187 min.

being given and in 1 during administration of DCA alone (Table 3). The subjects remained seated in a straight-backed chair during the first part of each experiment (135 to 330 minutes) and then lay flat in bed for the remaining hours of the study. They stood up only as required for weighing and urine collections. Two subjects receiving both cortisone and DCA excreted more sodium when reclining than they had while seated (Table 3, Exps. K-2, K-6 and C-3; Fig. 1). The third subject maintained a virtually constant rate of natriuresis when studied under these conditions (Exp.

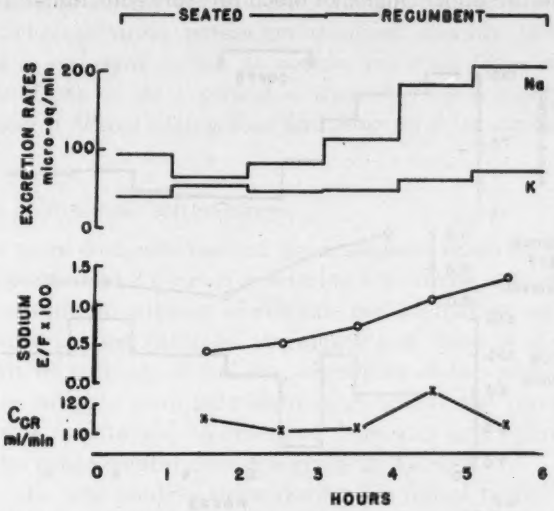

FIG. 1. (Experiment C-3.) Enhancement of renal sodium excretion with change from seated to recumbent posture.

M-3), whereas when she had been maintained on DCA alone without cortisone a progressive fall in sodium excretion took place despite change to the recumbent posture (Exp. M-2).[2]

In Experiment K-2 the augmentation of sodium excretion during recumbency was associated with a rise in endogenous creatinine clearance and estimated filtered sodium load. However, in the subsequent study, K-6, and in Subject D.C., sodium excretion increased similarly without significant change in creatinine clearance or filtered sodium. In all three experiments on these 2 subjects the estimated percentage of filtered sodium rejected by the tubules (sodium E/F×100) increased during

[2] Comparison of these two studies of Subject A.M. is difficult, since the initial rates of sodium excretion were quite different. At the time of the second study she had received cortisone for only five days and continued to exhibit a poor diuretic response to water loading.

recumbency. *Thus in 2 of the 3 patients taking cortisone a distinct rise in sodium excretion was demonstrated with change to recumbency without a concomitant rise in estimated filtered sodium load.*

II. *Venous congestion of the lower extremities*

The 1 subject in whom venous congestion of the legs was induced remained recumbent except during weighing and urine collection (Exp. K-5, Fig. 2). A two-hour control period after water loading was followed by application, to the upper thighs, of blood pressure cuffs inflated to maintain

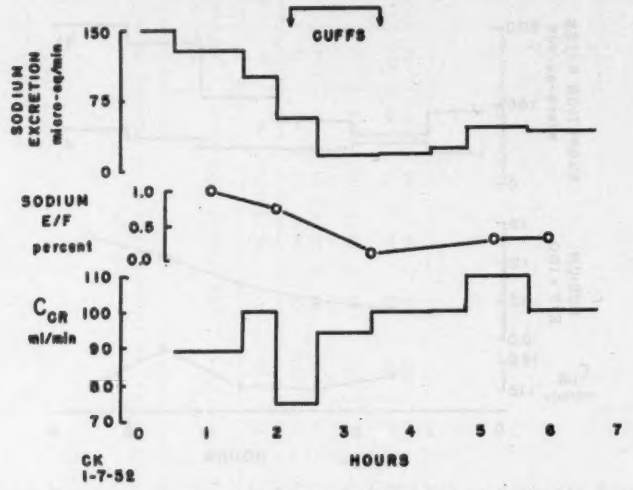

FIG. 2. (Experiment K-5). Decreased renal excretion of sodium with venous congestion of the lower extremities.

a pressure 5 to 10 mm. of mercury below the diastolic blood pressure for seventy-one minutes. Collections were continued for several hours after removal of the cuffs. Prior to the inflation of the cuffs there was a moderate decline in the rate of sodium excretion from 147 to 102 micro-eq. per minute. During venous congestion creatinine clearance initially fell and a further decline in sodium output took place. However, despite a return of creatinine clearance to its previous value during the latter half of the period of congestion and a subsequent rise to even higher values, the rate of sodium excretion continued to fall to 15 micro-eq. per minute and remained below 50 micro-eq. per minute during the last two hours. The decrease in natriuresis was thus dependent upon increased tubular reabsorption. The extreme reduction in sodium excretion was temporally related to venous congestion. Moreover, the magnitude of the decrease far exceeded

that which took place in the same subject when he was observed for a similar period of time without venous congestion. For example, in Exp. K-2 the rate of sodium excretion was 145 micro-eq. per minute during the first forty-one minutes, 110 micro-eq. per minute during the next fifty-nine minutes and then remained at 89 micro-eq. per minute for eighty-eight minutes.

During and after "cuffing," urine flow fell from its previous levels of 10.2–12.1 ml. per minute to a minimum value of 4.1 ml. per minute; subsequently rising to 7.5 ml. per minute. Chloride excretion paralleled that of sodium, whereas urine potassium declined steadily throughout the study. *Thus a prolonged decline in sodium excretion followed venous congestion of the thighs in the 1 patient so studied. This decline persisted long after the estimated filtered sodium load had returned to, or exceeded the initial value.*[3]

III. *Infusion of hypotonic salt solutions*

On two or more occasions each of the 3 subjects received intravenously over a two-hour period 2 liters of a solution containing approximately 115 milli-eq. of sodium, 90 milli-eq. of chloride and 25 milli-eq. of bicarbonate per liter. The breakfast eaten on the morning of these studies contained no more than 10 milli-eq. of sodium, regardless of the preceding dietary regimen. The patients were recumbent throughout the procedure and a water load was maintained as described here and in a previous publication (14). The experimental data are given in Table 4.

Subject C. K. was studied twice during his initial period of cortisone therapy, again after cortisone had been discontinued for thirty days, and finally after cortisone had been resumed for seven days. On all four occasions a rise in sodium excretion took place during or after the infusion. The

[3] A similar observation has been kindly communicated to us by Dr. Franklin H. Epstein, who studied a 54-year-old bilaterally adrenalectomized and orchiectomized man maintained on 50 mg. of cortisone intramuscularly and 3–5 mg. of DCA intramuscularly daily. During thirty minutes prior to venous congestion of the thighs, urine sodium excretion averaged 364 micro-eq./min. and inulin clearance 123 ml./min. During the second quarter hour of venous congestion the minimum value for inulin clearance observed, 87 ml./min., was associated with sodium excretion at a rate of 179 micro-eq./min. During the last half hour of "cuffing," inulin clearance rose to 100–104 ml./min. while sodium excretion continued to fall to 141 and 103 micro-eq./min. Thus, during the "cuffing period" a return of inulin clearance toward control values was associated with a continued fall in natriuresis. Moreover, the sodium excretion rate during the first forty-six minutes after releasing the cuffs averaged 165 micro-eq./min. and was associated with an inulin clearance of 110 ml./min; whereas during the first quarter hour of cuffing an almost identical inulin clearance (112 ml./min.) was associated with sodium excretion at the rate of 310 micro-eq./min.

TABLE 4. RENAL EXCRETION OF WATER AND SOLUTES WITH HYPOTONIC INFUSION OF SODIUM SALTS

Subject and Exp. No.	Cortisone therapy (days)	Elapsed time (min.)		Urine flow (ml./min.)		Rate of solute excretion (μEq./min.)						Urine Na (mEq./L.)		Creat. clear. (ml./min.)		Sodium (E/F×100)	
						Na		K		Cl							
		I*	II†	I	II	I	II	I	II	I	II	I	II	I	II	I	II
K-3	145	157–214	275–335	16.2	16.5	365	491	84	79	315	411	23	30	110	107	2.62	3.67
K-4	186	153–240	308–362	8.5	11.9	81	199	82	70	66	119	10	17	100	102	0.56	1.56
K-7	None‡	142–202	335–391	6.8	8.7	168	252	58	75	166	191	25	29	89	111	1.48	1.80
K-8	7§	158–219	277–362	9.0	14.0	142	408	52	118	123	310	16	29	90	100	1.24	3.21
C-1	None	100–160	310–435	0.9	0.9	45	28	63	49	89	51	52	32	71	95	0.47	0.22
C-2	21	98–193	376–437	2.6	4.1	84	179	78	62	125	144	32	44	100	97	0.65	1.45
M-1	None	80–160‖	320–400	0.4	0.6	21	55	49	17	31	32	53	99	54	73	0.25	0.59
M-4	8	135–195¶	315–375	9.7	10.3	103	140	114	42	120	84	11	14	77	82	1.02	1.31

* I—Period just prior to hypotonic infusion.
† II—Period of maximal sodium excretion during or after hypotonic infusion.
‡ Cortisone discontinued thirty days previously.
§ Cortisone resumed seven days previously.
‖ Includes first 25 minutes of infusion; sodium excretion unchanged throughout infusion period.
¶ Includes first 15 minutes of infusion; sodium excretion fell further to 79 μEq./min. during subsequent hour of infusion.

increments in natriuresis were of large magnitude, equal to or greater than those observed in 2 normal subjects who received infusions of the same volume (14). As in normal individuals chloride excretion increased, but less strikingly than sodium, and changes in potassium output were variable. Serum sodium concentration did not increase in any of these studies. In the two experiments carried out during the first course of cortisone (K-3, 4), renal clearance of creatinine remained essentially constant; whereas, when cortisone had been omitted, a significant increase in this clearance occurred after the infusion. Hence, the augmented rate of sodium excretion after infusion was associated with an increase in the estimated filtered sodium load in Experiment K-7, but not in the two preceding studies. An equivocal rise in creatinine clearance took place in Experiment K-8, in which the increase in natriuresis was the largest observed in this group of studies. Although in all four experiments the increased excretion of sodium represented an increase in E/F fraction, only when cortisone was being taken did E/F rise without augmentation of the filtration rate.

Subject D. C., prior to the institution of cortisone therapy, maintained a low urine flow after water loading and also after the hypotonic infusion was given. The urinary concentration of sodium and its excretion rate declined slowly during the experiment, despite an increase in creatinine clearance following the infusion (Exp. C-1, Table 4; Fig. 3). When a solution of the same volume and composition was infused after three weeks of cortisone therapy there was a marked increase in sodium excretion without a change in creatinine clearance or estimated filtered sodium load (Exp. C-2, Table 4; Fig. 3).

In the third patient a small rise in sodium excretion, together with a distinct increase in urinary sodium concentration followed infusion prior to cortisone therapy. There was a concomitant elevation of creatinine clearance. After eight days of cortisone therapy a modest rise in sodium excretion followed the infusion, without significant change in creatinine clearance (Exps. M-1 and M-4, Table 4).

Thus in all 3 subjects a hypotonic infusion containing approximately 115 milli-eq. of sodium, 90 milli-eq. of chloride and 25 milli-eq. of bicarbonate per liter evoked a natriuretic response. This response took place without an increase in estimated filtered sodium load, only when cortisone was being given.

IV. *Diurnal renal excretory rhythm*

Subject C. K. remained in bed over a period of eighty-four hours, during which he took identical meals every six hours. Each meal consisted of 240 ml. of milk, one cheese sandwich and one egg sandwich made up from single lots of salt-poor bread, salt-poor butter, cheddar cheese, eggs and mayonnaise. The sandwiches were all prepared in advance at one time, stored in a food freezer and thawed as required prior to each meal. At regular inter-

vals between these feedings the patient took additional fluids consisting of water and physiologic salt solution, so that every six hours he ingested a total of 56 milli-eq. of sodium, 16 milli-eq. of potassium and 750 ml. of water. After the patient had undergone a 24-hour period of adjustment to the regimen, complete urine collections were made during each six-hour

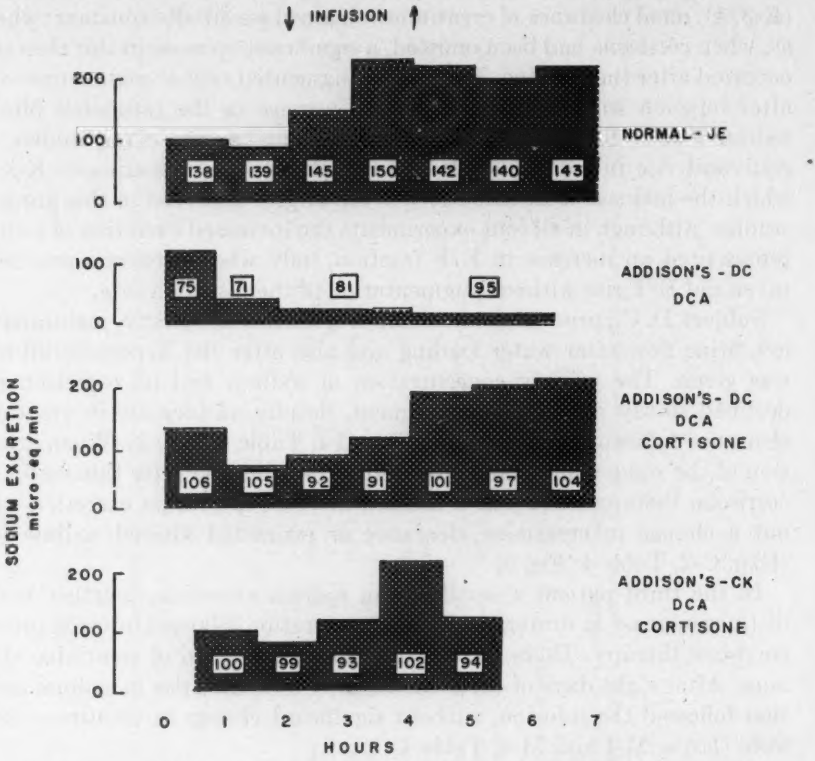

FIG. 3. Renal sodium excretion with infusion of hypotonic salt solutions. Endogenous creatinine clearance for each period superimposed on graph. Uppermost graph—normal subject previously reported (14). Second graph—Experiment C-1. Third graph—Experiment C-2. Fourth graph—Experiment K-4.

period for the last sixty hours of the study. Blood samples were taken at the beginning and end of each collection period for creatinine determinations.

A normal diurnal rhythm of the renal excretion of sodium, potassium, chloride and water was demonstrated (Exp. K-1, Fig. 4). On the first two nights of observation endogenous creatinine clearance was lower than by day, but on the third night its magnitude rose to 120 ml. per minute.

Although sodium excretion was higher on this night than on the previous two, it was far lower than during the first daytime period when creatinine clearance was identical. Moreover it remained below that of the second and third daytime periods during which creatinine clearances were 115 and 105 ml. per minute.

Hence, not only were the diurnal rhythms of water and electrolyte excretion of normal pattern, but the rhythm appeared to be independent of change in creatinine clearance, as in normal subjects (15, 16).

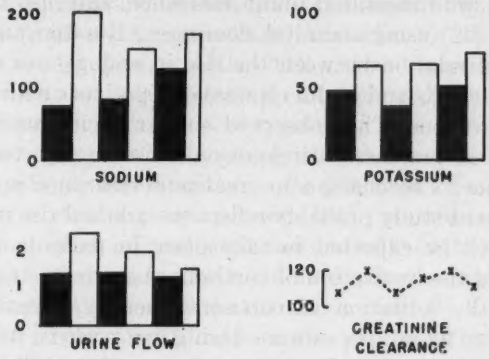

FIG. 4. (Experiment K-1.) Diurnal excretory pattern when identical food and fluid were taken every six hours with continuous recumbency. Black columns—6 P.M. to 6 A.M. Open columns—6 A.M. to 6 P.M. (third set of open columns—6 A.M. to 12 noon). Sodium and potassium excretion in μEq./min. Urine flow and creatinine clearance in ml./min.

DISCUSSION

The 2 patients who were studied after receiving cortisone replacement therapy for three weeks or longer exhibited appropriate responses to stimuli which characteristically induce acute change in renal sodium excretion in normal individuals. The third patient exhibited a modest natriuretic response to infusion of a hypotonic solution of sodium salts after only eight days of cortisone therapy. She manifested no rise in sodium excretion on changing from the seated to the recumbent posture after five days of therapy.[4] It is most unlikely that the observed changes in sodium excretion were mediated by endogenous adrenal hormone production. In all 3 patients the diagnosis of Addison's disease was based upon clear-cut clinical and laboratory evidence. It may be assumed that if any endogenous hormone were produced it would be an insignificant addition to the constant exogenous supply. Moreover the exogenous hormone would tend to suppress the activity of any remnants of adrenal cortex.

[4] We have observed several normal subjects who fail to exhibit a natriuretic response to postural change of this variety.

There is good evidence that changes in excretion or clearance of creatinine reflect changes in glomerular filtration rate, not only in normal subjects (17) but also in patients with Addison's disease. Marshall and Davis in 1916 demonstrated that adrenalectomized cats excreted creatinine loads very slowly (18). Margitay-Becht and Gömöri originally postulated lowering of filtration rate in patients with Addison's disease, on the basis of measurement of exogenous creatinine clearance (19). The validity of their inference was subsequently established by Talbott *et al.* (20) and Sanderson (21), who measured inulin clearance, and also by Waterhouse and Keutmann (22) using mannitol clearances. Burston and Garrod (23) found a close correlation between the rise in endogenous creatinine output over short periods and inulin clearance in patients with panhypopituitarism given cortisone. They observed similar rapid increments in creatinine excretion in patients with Addison's disease who took large single doses of cortisone. The changes in creatinine clearance noted in Subject D.C. of the present study probably reflect the gradual rise in filtration rate which might well be expected to take place in patients with Addison's disease following the institution of cortisone therapy in small doses. Eight days prior to the initiation of cortisone therapy, creatinine clearance ranged from 71 to 95 ml. per minute during five periods. After twenty-one days of therapy the range in seven periods was 91 to 109 ml. per minute. One week later the range was 109 to 122 ml. per minute. On the other hand, no increase in creatinine clearance was observed in Subject A.M., perhaps because studies were continued for only eight days after she was started on small doses of cortisone.

On the basis of the evidence summarized in the preceding paragraph it seems justifiable to infer that changes in filtration rate would be reflected by changes in endogenous creatinine clearance, even though the studies of Burnett (24) demonstrated small differences between inulin and creatinine clearance in subjects receiving large doses of cortisone. In the present study the acute changes observed in sodium excretion usually occurred without parallel changes in creatinine clearance, and consequently are not ascribable to altered filtration. It is noteworthy that the preponderance of evidence supports the view that in normal subjects alterations in sodium excretion induced by stimuli such as change in posture, venous congestion, or expansion of extracellular volume do not require change in filtered sodium load (25). Furthermore it appears unlikely that the diurnal rhythm of sodium excretion is dependent on altered filtration (15, 16). It would be surprising if patients with Addison's disease responded to a variety of stimuli by changing renal excretion of sodium in a normal way, but by a mechanism not operative in the normal. The studies of Burnett *et al.* (26) concerning the response of a patient with Addison's disease to progressive increments in oral salt intake support the view that appropriate

renal adjustments can take place without changes in hormonal supply and that the renal mechanism is not dependent on change in glomerular filtration as measured by inulin clearance.

The capacity of the patients with Addison's disease to regulate sodium excretion in an apparently normal manner while receiving DCA plus cortisone may be contrasted with the decreased ability of the untreated patient to conserve sodium or to deliver large salt loads rapidly (24, 27, 28), and with the tendency of patients treated with DCA alone to retain excessive amounts of salt when intake is high (29). The overall impairment of renal function characteristic of patients with Addison's disease and only partially corrected by therapy with DCA and salt may be an important factor. Cortisone appears to correct these abnormalities, at least in primary adrenal insufficiency.

The demands of proper clinical management limited the comparisons we could make in patients before and after the initiation of cortisone therapy. However, it seems clear that one patient (D.C.) manifested no increase in sodium excretion when infused with sodium salts in hypotonic solution while receiving DCA alone, but behaved normally when the procedure was repeated after cortisone therapy. In another patient (C.K.) withdrawal of cortisone for four weeks after it had been given for more than eight months did not abolish his natriuretic response to the hypotonic infusion, but on this occasion there was a rise in creatinine clearance, not observed when cortisone was being given. Moreover, at this time he also continued to exhibit a brisk diuretic response to ingested water—a response rarely observed in patients with Addison's disease except during cortisone therapy. That the influence of cortisone upon the kidney may persist for some time after its administration is discontinued is suggested by observations concerning its effects upon the diurnal excretory rhythm (16, 26). Hence the appropriate natriuretic response observed in this subject after cortisone had been withdrawn may have been related to change in filtration rate or to preservation of renal tubular responsiveness consequent to antecedent cortisone administration.

Because they found that the hypernatremia induced in rats by DCA was diminished by concurrent administration of adrenocortical extract or corticotropin, Woodbury and co-workers proposed that the 11-oxygenated steroids might act to "normalize" serum sodium concentration (30). The authors suggested that these steroids " . . . initiate processes which tend to correct either an excess or deficiency of sodium." Inasmuch as their DCA-treated animals had adrenal atrophy, the observations are also consistent with the alternative hypothesis that deficiency of 11-oxysteroids impairs processes or mechanisms which in normal animals tend to correct an excess or deficiency of sodium. A similar interpretation can be placed upon the observations of Thorn (31, 32), who noted that patients with

Addison's disease maintained on DCA might manifest a moderate diuresis of sodium and water when cortisone therapy was begun.[5] An attempt was made to explain this "paradoxical" effect of cortisone by postulating competition at the renal tubule cell between the weakly salt-retaining cortisone and the strongly salt-retaining DCA. It would now seem more reasonable to suppose that cortisone restores the ability of such patients to deliver slight excesses of sodium and water which may be clinically inapparent. These formulations are in keeping with the broad concept of the permissive action of adrenocortical hormones, so clearly formulated and developed by Ingle (9, 10).

Our observations do not argue against the hypothesis that cortical hormones, particularly aldosterone, may not be the essential mediators of renal salt conservation in various circumstances. For example, increased amounts of salt-retaining steroids have been found in the urine of edematous patients by various investigators and recently it has been reported that normal subjects rendered salt-deficient excrete increased amounts of material resembling "electrocortin" (7, 8). It may be, as suggested by the experiments of Davis and Howell, that pronounced, continued inhibition of sodium excretion requires increased salt-retaining adrenocortical hormone activity (33). However, our study may not apply to the mechanisms of salt retention in edematous states or salt depletion. All subjects had normal serum levels of sodium when studied and none was dehydrated or edematous while receiving cortisone. In the absence of such circumstances, acute changes in sodium excretion of considerable magnitude appeared to be independent of *changes* in adrenocortical hormone level, although cortisone appeared to *maintain* the integrity of the regulatory mechanisms involved.

SUMMARY AND CONCLUSIONS

The response to stimuli which evoke changes in renal sodium excretion in normal subjects was studied in 3 patients with Addison's disease while they received cortisone and DCA.

In 2 patients renal sodium excretion varied with change in posture, but in the third, who had received cortisone for only five days, no definite response was evident.

The 1 patient who was tested exhibited a decline in natriuresis during and after venous congestion of the thighs.

In all 3 patients increased sodium excretion followed infusion of a hypotonic solution of sodium salts.

[5] One of our patients (D.C.) had minimal pretibial edema while taking 6 mg. of DCA daily with salt *ad libitum*. During the first eight days after cortisone was added to his regimen he lost 2.3 kilos and the edema disappeared.

A normal diurnal excretory rhythm for water and electrolyte was demonstrated in the 1 patient so studied.

Changes in sodium excretion were related to alterations in tubular reabsorption rather than in filtered sodium load.

Although cortisone appeared to *maintain* the integrity of the regulatory mechanisms for sodium excretion in these patients, the *changes* in sodium excretion were presumably independent of change in hormone activity.

Acknowledgments

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REFERENCES

1. Rosenbaum, J. D.; Papper, S., and Ashley, M. M.: Variations in renal tubular re-Absorption of sodium independent of change in adrenocortical hormone, (abstract) *J. Clin. Invest.* **31**: 657, 1952.
2. Loeb, R. F.: Chemical changes in the blood in Addison's disease, *Science* **76**: 420, 1932.
3. Loeb, R. F.: Effect of sodium chloride in the treatment of a patient with Addison's disease, *Proc. Soc. Exper. Biol. & Med.* **30**: 808, 1933.
4. Loeb, R. F.; Atchley, D. W.; Benedict, E. M., and Leland, J.: Electrolyte balance studies in adrenalectomized dogs with particular reference to the excretion of sodium, *J. Exper. Med.* **57**: 775, 1933.
5. Leaf, A., and Couter, W. T.: Evidence that renal sodium excretion by normal human subjects is regulated by adrenal cortical activity, *J. Clin. Invest.* **28**: 1067, 1949.
6. Black, D. A. K.; Platt, R., and Stanbury, S. W.: Regulation of sodium excretion in normal and salt-depleted subjects, *Clin. Sc.* **9**: 205, 1950.
7. Axelrad, B. J., and Luetscher, J. A., Jr.: Adrenal cortical activity in normal men on diets of low sodium content, *J. Clin. Invest.* **33**: 916, 1954.
8. Luetscher, J. A., Jr., and Johnson, B. B.: Observations on the sodium-retaining corticoid (aldosterone) in the urine of children and adults in relation to sodium balance and edema, *J. Clin. Invest.* **33**: 1441, 1954.
9. Ingle, D. J.: The functional interrelationship of the anterior pituitary and the adrenal cortex, *Ann. Int. Med.* **35**: 652, 1951.
10. Ingle, D. J.: The role of the adrenal cortex in homeostasis, *J. Endocrinol.* (British) **8**: 23, 1952.
11. Gornal, A. G.; Bardawill, C. J., and David, M. M.: Determination of serum proteins by means of the biuret reaction, *J. Biol. Chem.* **177**: 751, 1949.
12. Strauss, M. B.; Davis, R. K.; Rosenbaum, J. D., and Rossmeisl, E. C.: "Water diuresis" produced during recumbency by the intravenous infusion of isotonic saline solution, *J. Clin. Invest.* **30**: 862, 1951.
13. Rosenbaum, J. D.; Nelson, W. P., III; Strauss, M. B.; Davis, R. K., and Rossmeisl, E. C.: Variation in the diuretic response to ingested water related to the renal excretion of solutes, *J. Clin. Invest.* **32**: 394, 1953.
14. Strauss, M. B.; Davis, R. K.; Rosenbaum, J. D., and Rossmeisl, E. C.: Production of increased renal sodium excretion by the hypotonic expansion of extracellular fluid volume in recumbent subjects, *J. Clin. Invest.* **31**: 80, 1952.

15. Sirota, J. H.; Baldwin, D. S., and Villarreal, H.: Diurnal variations of renal function in man, *J. Clin. Invest.* **29**: 187, 1950.
16. Rosenbaum, J. D.; Ferguson, B. C.; Davis, R. K., and Rossmeisl, E. C.: The influence of cortisone upon the diurnal rhythm of renal excretory function, *J. Clin. Invest.* **31**: 507, 1952.
17. Brod, J., and Sirota, J. H.: The renal clearance of endogenous "creatinine" in man, *J. Clin. Invest.* **27**: 645, 1948.
18. Marshall, E. K., and Davis, D. M.: The influence of the adrenals on the kidneys, *J. Pharmacol. & Exper. Therap.* **8**: 525, 1916.
19. Margitay-Becht, E., and Gömöri, P.: Die Nierenfunktion bei der Addisonschen Krankheit, *Ztschr. f. d. ges. exper. Med.* **104**: 22, 1938.
20. Talbott, J. H.; Pecora, L. J.; Melville, R. S., and Consolazio, W. V.: Renal function in patients with Addison's disease and in patients with adrenal insufficiency secondary to pituitary panhypofunction, *J. Clin. Invest.* **21**: 107, 1942.
21. Sanderson, P. H.: Renal function in Addison's disease, *Clin. Sc.* **6**: 197, 1948.
22. Waterhouse, C., and Keutmann, E. H.: Kidney function in adrenal insufficiency, *J. Clin. Invest.* **27**: 372, 1948.
23. Burston, R. A., and Garrod, O.: The variability of the lowered glomerular filtration rate in Addison's disease and panhypopituitarism, and the effect of cortisone thereon, *Clin. Sc.* **11**: 129, 1952.
24. Burnett, C. H.: The actions of ACTH and cortisone on renal function in man, *in* Renal Function. Transactions of the Second Conference, (1950), edited by Bradley, S. E. New York, Josiah Macy, Jr. Foundation. 1951, p. 106.
25. Selkurt, E. E.: Sodium excretion by the mammalian kidney, *Physiol. Rev.* **34**: 287, 1954.
26. Burnett, C. H.; Seldin, D. M., and Walser, M.: Observations on the electrolyte and water metabolism in Addison's disease during oral salt loading, *Tr. A. Am. Physicians* **66**: 65, 1953.
27. Willson, D. M., and Sunderman, F. W.: Studies in serum electrolytes. XII. The effect of water restriction in a patient with Addison's disease receiving sodium chloride, *J. Clin. Invest.* **18**: 35, 1939.
28. Reforzo-Membrives, J.; Power, M. H., and Kepler, E. J.: Studies on the renal excretion of water and electrolytes in cases of Addison's disease, *J. Clin. Endocrinol.* **5**: 76, 1945.
29. Thorn, G. W., and Firor, W. M.: Desoxycorticosterone acetate therapy in Addison's disease. Clinical considerations, *J.A.M.A.* **114**: 2517, 1940.
30. Woodbury, D. M., Cheng, C. P.; Sayers, G., and Goodman, L. S.: Antagonism of adrenocorticotrophic hormone and adrenal cortical extract to desoxycorticosterone; electrolytes and electroshock threshold, *Am. J. Physiol.* **160**: 217, 1950.
31. Thorn, G. W.; Forsham, P. H.; Bennett, L. L.; Roche, M.; Reiss, R. S.; Slessor, A.; Flink, E. B., and Somerville, W.: Clinical and metabolic changes in Addison's disease following the administration of compound E acetate, *Tr. A. Am. Physicians* **62**: 233, 1949.
32. Thorn, G. W.: Further clinical studies with ACTH and adrenal cortical hormones, *in* Adrenal Cortex. Transactions of the Second Conference (1950), edited by Ralli, E. P. New York, Josiah Macy, Jr. Foundation. 1951, p. 164.
33. Davis, J. O., and Howell, D. S.: Diuresis during maintenance of adrenalectomized dogs with ascites on cortisone, *Endocrinology* **53**: 653, 1953.

EFFECT OF INTRAVENOUS INJECTION OF FRUCTOSE, WITH AND WITHOUT ACTH ADMINISTRATION, ON THE LEVEL OF BLOOD GLUCOSE*

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IT IS well known that intravenously administered fructose disappears from the blood faster than glucose in normal subjects. Moreover, diabetic patients are able to utilize fructose better than glucose without insulin (1–7) It is also known that the metabolism of glucose is inhibited by adrenocortical stimulation, the result of which is an inhibition of insulin which stops the synthesis of hexose-phosphate through the hexokinase reaction (8). These observations suggest the hypothesis that the metabolism of fructose, which does not need insulin, it not inhibited by adrenocortical stimulation. On the other hand, if fructose is transformed into glucose in the organism, adrenocortical stimulation might bring about a hyperglycemia after fructose injection, because of the anti-insulin effect of this stimulation. The experiments reported here were carried out to test these two hypotheses.

MATERIAL AND METHODS

A 10 per cent solution of fructose in normal saline was injected intravenously during a period of sixty minutes into 13 subjects—10 normal and 3 diabetic. The total amount of fructose administered varied from 0.9 Gm. to 1.2 Gm. per Kg. of body weight.

The subjects were in the postabsorbtive phase and kept at bed rest during the whole experimental period.

The normal subjects were people well along in the convalescent period of benign infectious disease, or were hospitalized for social reasons. They presented no evidence of disease by ordinary physical and laboratory examinations. In the 3 diabetics the disease was of the usual adult type. They all had consistently elevated fasting blood sugar levels and their glucose tolerance curves were of the diabetic type. These patients were not treated before, nor otherwise during the experimental period, and were not receiving insulin.

Blood fructose and glucose levels were determined on venous blood before the infusion of fructose solution and at 30, 60, 120 and 180 minutes after the beginning of the infusion.

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Urine samples were collected by complete voluntary voiding before and at the end of the infusion, as well as 120 minutes after the end of the infusion. The amount of fructose and glucose was measured in each sample.

In all 13 subjects, the infusion was repeated twenty-four hours later. Previous to the second infusion, a total amount of 50 units of ACTH[1] was given to each subject in 5 separate intramuscular injections of 10 units each, at four-hour intervals, the last injection being given at 6 A.M. The infusion of fructose was then started at 9 A.M.

Total reducing sugar was determined in blood and urine samples by Shaffer-Hartman's method (9). Fructose was measured by Roe's method (10). The amount of glucose was obtained by substracting the levulose value from that for the total reducing sugar.

In addition to the 13 subjects, a group of 3 additional normal subjects was used in control experiments in which intravenous injections of physiologic saline without fructose were given. The effects on blood glucose and fructose levels were studied.

RESULTS

Blood levels

I. *Normal subjects* (Table 1)

a. *Without ACTH.* When fructose was administered to 10 normal subjects, the highest average blood fructose level for the group was 68 mg. per 100 cc. and this was reached half an hour after the injection. The average blood level returned to zero after three hours. Individual blood levels after half an hour varied from a low of 37 to a high of 104 mg. per 100 cc.

At the same time the blood glucose level, on the average, rose from 97 mg. per 100 cc. before the infusion of fructose to 102 mg. half an hour, and 101 mg. one hour after the infusion. In individual cases, the highest elevation was 20 mg. (Subject No. 4.) In several subjects there was almost no variation of the blood glucose level after the infusion of fructose (Nos. 1, 2, 3, 7 and 10).

b. *With ACTH.* When the fructose infusion was repeated on the same subjects following the administration of ACTH, the levels of blood fructose did not differ to any significant extent from those observed when no ACTH was given. However, the average glucose level, under these conditions, rose from a control value of 117 mg. per 100 cc. of blood to a high of 144 mg. one hour after the infusion. In individual patients, the greatest elevation of the blood glucose level following ACTH and the infusion of fructose was 51 mg. (Subject No. 9, one-hour sample) and there was an increase of more than 15 mg. in 7 out of 10 subjects (Nos. 3, 4, 5, 6, 7, 9 and 10).

Statistical analysis of the blood glucose levels observed after the infusion of fructose preceded by the administration of ACTH, when compared to

[1] Cortrophin, Organon. The response to this preparation was controlled in normal subjects and in diabetics by eosinophil counts and 17-ketosteroid measurements (11).

TABLE 1. EFFECT OF INTRAVENOUS INFUSION OF FRUCTOSE ON BLOOD LEVELS OF FRUCTOSE AND GLUCOSE IN NORMAL SUBJECTS, WITH AND WITHOUT INJECTION OF ACTH

Subjects	*Without ACTH*										*After ACTH*									
	Fructose levels (mg./100 cc.)					Glucose levels (mg./100 cc.)					Fructose levels (mg./100 cc.)					Glucose levels (mg./100 cc.)				
	Control	½ h.	1 h.	2 h.	3 h.	Control	½ h.	1 h.	2 h.	3 h.	Control	½ h.	1 h.	2 h.	3 h.	Control	½ h.	1 h.	2 h.	3 h.
1. Wa	0	52	45	0	0	83	87	84	79	82	0	38	40	0	0	101	108	107	108	104
2. He	0	81	72	8	0	93	94	97	83	89	0	52	70	2	0	113	128	129	103	124
3. Mu	0	58	68	3	0	98	97	80	88	97	0	71	40	3	0	106	109	152	105	104
4. Da	0	78	85	9	3	110	130	131	90	95	0	84	72	5	1	140	158	163	121	119
5. Du	0	104	88	5	0	95	102	110	99	91	0	71	89	7	0	122	136	159	133	120
6. De	0	67	68	7	0	104	118	123	93	95	0	76	85	7	2	113	133	137	112	118
7. Bo	0	73	63	5	0	86	81	86	79	78	0	58	46	5	0	132	142	150	129	128
8. Dy	0	37	59	4	0	111	108	104	104	108	0	52	55	6	0	145	151	152	146	128
9. Bi	0	74	71	5	0	97	110	104	70	78	0	67	63	5	0	94	123	145	94	81
10. Al	0	56	53	4	0	93	95	91	86	84	0	57	56	5	0	104	137	142	111	92
Average	*0*	*68*	*67*	*5*	*0*	*97*	*102*	*101*	*87*	*90*	*0*	*63*	*62*	*5*	*0*	*117*	*132*	*144*	*116*	*112*

TABLE 2. EFFECT OF INTRAVENOUS INFUSION OF FRUCTOSE ON BLOOD LEVELS OF FRUCTOSE AND GLUCOSE IN DIABETICS WITH AND WITHOUT INJECTION OF ACTH

Subjects	*Without ACTH*										*After ACTH*									
	Fructose levels (mg./100 cc.)					Glucose levels (mg./100 cc.)					Fructose levels (mg./100 cc.)					Glucose levels (mg./100 cc.)				
	Control	½ h.	1 h.	2 h.	3 h.	Control	½ h.	1 h.	2 h.	3 h.	Control	½ h.	1 h.	2 h.	3 h.	Control	½ h.	1 h.	2 h.	3 h.
11. Re	0	61	48	4	0	262	309	343	319	288	0	60	57	4	0	324	371	418	364	352
12. Bq	0	83	87	13	4	240	259	263	271	272	0	75	60	0	0	332	342	358	357	334
13. Ho	0	58	60	7	3	350	401	416	379	356	0	76	60	7	3	333	361	403	377	379
Average	*0*	*67*	*65*	*8*	*2*	*284*	*323*	*341*	*323*	*305*	*0*	*70*	*59*	*4*	*1*	*330*	*358*	*393*	*366*	*355*

the corresponding values observed without ACTH administration, revealed a high degree of significance of the results:

$$t = 3{,}512^{zz}$$

II. *Diabetics* (Table 2)

The average value for fructose blood levels after the infusion of fructose did not differ significantly, regardless of ACTH administration, and did not differ from the average values obtained in normal subjects.

In the diabetic group, there was an average elevation of the blood glucose level of 57 mg. without ACTH, as compared to 63 mg. when ACTH was given. The difference was not significant.

III. *Control experiments* (Table 3)

Control experiments, using an infusion of physiologic sodium chloride in 3 normal individuals, failed to reveal any effect on the blood glucose levels.

TABLE 3. BLOOD GLUCOSE LEVELS (MG./100 CC.) DURING CONTROL EXPERIMENTS WITH ACTH AND PHYSIOLOGIC SALINE IN NORMAL SUBJECTS

Subjects	*Without ACTH*					*After ACTH*				
	Control	½ h.	1 h.	2 h.	3 h.	Control	½ h.	1 h.	2 h.	3 h.
1	108	99	91	93	102	115	109	105	118	—
2	81	81	82	83	82	102	102	98	98	99
3	88	78	88	85	84	100	98	102	106	101
Average	*92*	*86*	*87*	*87*	*89*	*106*	*103*	*102*	*107*	—

Urinary excretion

The urinary excretion of fructose in all individuals was below 5 per cent of the total amount injected and did not vary after administration of ACTH in normal subjects or in the diabetics.

DISCUSSION

The data show that intravenously administered fructose is rapidly removed from the blood in normal subjects and in diabetics. This is in agreement with previous reports.

In normal subjects and diabetics, the fructose level did not appear to be higher after one hour than after half an hour, which shows that withdrawal of fructose from the blood proceeded at the same rate as that of administration.

In general, there was little or no elevation of the blood glucose levels

after the administration of fructose. This is contrary to the observations of Weinstein and Roe (7), who concluded that normally a large portion of the fructose is converted into glucose. On the other hand, our data demonstrate a marked rise of the blood glucose level after injection of fructose into the 3 diabetic patients, even without ACTH administration. This is in agreement with the results published by Miller *et al.* (4).

As far as the effect of ACTH is concerned, our data show little or no effect from the adrenal stimulation on the blood fructose levels, in diabetics as well as normal subjects. After such adrenal stimulation, however, the injection of fructose resulted in statistically significant elevation of blood glucose levels in the normal subjects.

The hyperglycemia following fructose administration in diabetics was apparently unchanged after the administration of ACTH.

The mechanism of the hyperglycemia induced by fructose injection into normal subjects after ACTH administration is not explained by our data. Since, according to Slein *et al.* (12) and Stewart and Thompson (13), fructose can be converted into glucose in the liver and kidney, it would appear from our data that this conversion is enhanced when the adrenal cortex is stimulated. An alternative explanation of the hyperglycemia described here could be found in the anti-insulin activity of ACTH: the glucose normally formed from the injected fructose would induce a hyperglycemia only in those subjects receiving ACTH, because of the specific anti-insulin activity resulting from the adrenal stimulation. If this last explanation be correct, the administration of ACTH prior to the injection of fructose could be considered as a way of demonstrating glucose production from fructose in the body. The role of endogenous insulin in masking the hyperglycemia after fructose injection into normal subjects without ACTH, appears to receive confirmation from the observed hyperglycemia in our diabetics after such injection, even without ACTH: diabetics cannot respond to an increased demand for insulin as do normal subjects.

The observations reported here have a practical consequence. In conditions of stress, as following surgical operations, acute medical diseases and particularly diabetic coma (states accompanied by adrenal stimulation), large amounts of glucose may appear in blood after the administration of fructose. This will not be suspected if glucose determinations are not carried out after such administration. The rapid disappearance of fructose from the blood, under these conditions, gives no indication of the status of the total blood sugar level.

SUMMARY

1. *In normal subjects* intravenous injection of fructose did not induce an elevation of the blood glucose level. However, hyperglycemia was regularly induced when ACTH was given prior to fructose.

2. The rate of removal of fructose from the blood was not affected by prior administration of fructose.

3. *In diabetics* fructose was normally removed from the blood, regardless of the administration of ACTH.

4. Elevation of the blood glucose level resulted from the administration of fructose with or without ACTH.

5. It is concluded that the hyperglycemia following administration of ACTH to normal subjects receiving fructose indicates the conversion of fructose into glucose in the body.

6. The importance is emphasized of measuring the blood glucose level of patients who are in conditions of stress and receiving fructose intravenously.

REFERENCES

1. Bertino, J.; Dawson, N.; French, R.; Margen, S., and Kinsell, L. W.: Comparative observations regarding utilization and excretion of infused glucose, fructose and invert sugar, respectively, *J. Clin. Endocrinol. & Metab.* **13**: 658, 1953.
2. Craig, J. W.; Drucker, W. R.; Miller, M.; Owens, J. E., and Woodward, H., Jr.: The metabolism of fructose in the liver of normal and diabetic subjects, *J. Lab. & Clin. Med.*, **38**: 800, 1951.
3. Darragh, J. H.; Womersley, R. A., and Meroney, W. H.: Fructose in the treatment of diabetic ketosis, *J. Clin. Invest.* **32**: 1214, 1953.
4. Miller, M.; Drucker, W. R.; Owens, J. E.; Craig, J. W., and Woodward, H., Jr.: Metabolism of intravenous fructose and glucose in normal and diabetic subjects, *J. Clin. Invest.* **31**: 115, 1952.
5. Smith, L. H., Jr.; Ettinger, R. H., and Selingson, D.: A comparison of the metabolism of fructose and glucose in hepatic disease and diabetic mellitus, *J. Clin. Invest.* **32**: 273, 1953.
6. Weichselbaum, T. E.; Elman, R., and Lund, R. H.: Comparison utilization of fructose and glucose given intravenously, *Proc. Soc. Exper. Biol. & Med.* **75**: 816, 1950.
7. Weinstein, J. J., and Roe, J. H.: The utilization of fructose by human subjects and animals, *J. Lab. & Clin. Med.* **40**: 39, 1952.
8. Colowick, S. P.; Cori, G. T., and Slein, M. W.: The effect of adrenal cortex and anterior pituitary extracts and insulin on the hexokinase reaction, *J. Biol. Chem.* **168**: 583, 1947.
9. Peters, J. P., and Van Slyke, D. D.: Quantitative Clinical Chemistry. Baltimore, The Williams & Wilkins Co., 1932, vol. II, p. 466.
10. Roe, J. H.; Epstein, J. H., and Goldstein, N. P.: A photometric method for the determination of inulin in plasma and urine, *J. Biol. Chem.* **178**: 839, 1949.
11. Tagnon, R.: L'activité corticosurrénale au cours du diabète et de ses complications, *Acta clin. Belg.* **8**: 103, 1953.
12. Slein, M. W.; Cori, G. T., and Cori, C. F.: A comparative study of hexokinase from yeast and animal tissues, *J. Biol. Chem.* **186**: 763, 1950.
13. Stewart, C. P., and Thompson, J. C.: The conversion of levulose and fatty acids into glucose, *Biochem. J.* **35**: 245, 1941.

THE METABOLISM OF IODINE IN CEREBROSPINAL FLUID*†

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LITTLE attention has been paid to the penetration of thyroid hormone into cerebrospinal fluid (CSF), although the marked effect of thyroid hormone on the growth, development and function of the central nervous system is well documented. Congenital absence of thyroid hormone may result in the permanently impaired intellect of cretinism. Even adult myxedema results in marked dulling of mental activity, personality changes and occasionally frank psychosis (1). Conversely, overabundance of thyroid hormone, as in Graves' disease, results in mental agitation and occasionally manic or toxic psychosis (2, 3).

In myxedema, cerebral blood flow is decreased and cerebral vascular resistance is increased (4, 5). Whether there is a decrease in cerebral oxygen and glucose consumption is in dispute (4, 5). Myxedema causes characteristic changes in the electroencephalogram, consisting of a low voltage, slow frequency, absence of alpha waves, and absence of reaction to light stimulus (5).

In hyperthyroidism, cerebral oxygen and glucose consumption are unaltered (4, 6, 7). Increased cerebral blood flow and decreased cerebral vascular resistance have been reported (4, 6), but not by all workers (7). Abnormalities in the electroencephalogram in hyperthyroidism have been demonstrated (8).

The iodine content of CSF has received relatively slight attention.

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Gildea and Man (9) found an average CSF total iodine concentration of 0.2 γ per 100 ml. in 6 normal human patients. In 8 other patients, after the ingestion of Lugol's solution, when the total iodine of serum was increased to more than 100 γ per 100 ml., only a 1 to 6 per cent rise occurred in CSF.

Greenberg and associates (10) studied in dogs the passage of radioiodide and other ions from the serum into CSF. The order of permeability into CSF of the various halides was found to correspond inversely to the order of their ionic diameters, ($Cl^- > Br^- > I^-$). Iodide concentration in cisternal CSF achieved a constant level in one to two hours. When at apparent equilibrium with serum iodide, CSF iodide showed a concentration of only 12 per cent of the serum value.

The concentration of thyroxine and triiodothyronine in brain tissue has been found by several workers to be extremely low compared to the concentrations in most of the other body tissues (11, 12, 13). The problem of thyroid hormone in brain tissue is, however, quite distinct from that in CSF, and will not be considered here in detail.

No reports are available concerning the identification of thyroid hormone or other organic iodine compounds in CSF. The purpose of the present study is to measure the concentration in CSF of inorganic iodide and of any organic iodine-containing compounds that may be present.

METHODS

Samples of radioactive CSF and blood were obtained from patients at the Memorial Center who had received radioiodine (I^{131}) for the treatment of thyroid carcinoma, hyperthyroidism, or heart disease. The patients with thyroid cancer received doses in the range of 50 to 300 millicuries. Those with hyperthyroidism or heart disease received 20 to 30 millicuries. Clinical data on these patients are given in Table 1. Spinal fluid (10–25 ml.) was withdrawn by lumbar puncture. Serum protein-bound iodine (PBI) determinations were made by a modification of the method of Barker (14, 15).

In 5 patients the metabolism of inorganic iodide was studied. Samples of serum and CSF in this group were withdrawn within the first eight hours after administration of the isotope.

In 6 other patients, blood and CSF samples were withdrawn forty-eight hours after administration of the isotope, for the study of organic iodine compounds. In general, the patients who received the larger doses of radioiodine were included in the latter group, since the techniques for organic analysis demanded somewhat higher levels of radioactivity.

Two patients with mammary carcinoma who were clinically euthyroid received tracer doses of radioactive *l*-thyroxine intravenously. Samples of blood and CSF were withdrawn at forty-eight hours.

To determine at any time the ratio of total radioactivity in CSF compared to that in serum, an aliquot (1–3 ml.) of CSF was counted in a well-type scintillation counter against an equal volume of a 1:50 or 1:100 dilution of the serum.

To determine the fraction of radioactivity in CSF which was dialyzable, a measured sample (3–5 ml.) of a 1:10 dilution of the fluid was dialyzed by the method described

TABLE 1. CLINICAL AND I^{131} DATA

Patient	BMR (%)	Serum PBI (γ/100 ml.)	CSF protein (mg./100 ml.)	CSF pressure: (init; final) (mm. CSF)	I^{131} dose (mc.)	48-hr. I^{131} ur. excretion (% of dose)	Time of samples (hrs. after dose)	Ratio of tot. I^{131} (ser./CSF)	Ratio of iodide I^{131} (ser./CSF)
M.H. Recurr. Graves' dis.; 2 partial thyroidectomies.	+6 +39	9.8	37.8	125; 85	26*	42.5	2.0	103.5	103.5
H.K. Arterioscler. heart dis.; euthyroid.	−20 −3	4.7	52.4	125; 85	30	48.3	2.5	88.7	88.7
B.R. Graves' dis.; propylthiouracil 3 yrs.; no surgery.	+10, −7, +39	10.7	16.3	125; 50	12	19.8	4.0	62.9	62.9
G.T. Thyroid cancer; partial thyroidectomy; cerebral & skel. metast.	+22, +5, +9	1.9	50.6	370; 360	50	75.1	7.5	44.0	44.0
M.D. Recurr. Graves' dis.; partial thyroidectomy.	+17	7.0	37.4	—	30	39.1	8.0	113.0	113.0
E.G. Thyroid cancer; athyreotic; cerv. metast.; Tapazole 6 wks.	−2, +20, +16	2.5	37.9	95; 35	125	65.3	48.0	133.0	—
R.N. Thyroid cancer; 2 partial thyroidectomies; cerv. and mediast. metast.	—	1.4	30.2	200; 60	125	91.4	48.0	400.0	57.1
L.L. Thyroid cancer; athyreotic; pulm. metast.; Tapazole 8 wks.	—	1.1	38.2	360; 140	200	51.0	48.0	153.0	99.5
R.S. Thyroid cancer; athyreotic; pulm. metast.; Tapazole 6 wks.	−26	0.1	39.5	350; 190	125	57.8	96.0	—	—
A.L. Graves' dis.	—	10.4	37.5	55; 30	20	34.4	48.0	92.7	23.2
R.R. Rheum. heart dis.; intractable failure with anasarca.	—	7.5	—	—	25	30.6	48.0	97.5	—
B.C. Metastatic breast cancer; clinically euthyroid.	—	2.9	16.9	100; 60	—†	—	48.0	54.3	—
M.W. Metastatic breast cancer; euthyroid.	—	6.0	28.3	165; 35	—‡	—	48.0	78.6	—

* I^{133}.
† I.v. radiothyroxine tracer, with 41 gamma of carrier thyroxine.
‡ I.v. radiothyroxine tracer, with 48 gamma of carrier thyroxine.

subsequently for the concentration of CSF. The loss of radioactivity from the samples was evaluated by measuring them in a scintillation counter, using as standards, identical but undialyzed volumes of the same solution.

For the analysis of organic compounds, CSF was concentrated 50- to 100-fold. From 8 to 20 cc. of CSF was dialyzed in Visking tubing for twenty-four hours at 4° C. against two 3-liter volumes of a potassium phosphate buffer, 0.001 M, pH 6.6. The dialyzed fluid was lyophilized and the resulting white powder dissolved in 0.1 or 0.2 ml. of distilled water.

The concentrated CSF was analyzed by paper chromatography and electrophoresis. Ascending one-dimensional chromatography was conducted on Whatman No. 1 filter paper in two butanol solvent systems, one acid, and one ammoniacal, as previously described (16). A third system consisted of collidine:water, 100:35.5, in an atmosphere of concentrated ammonium hydroxide. Stable amino-acid carriers were streaked at the origin of the chromatograms and 0.01–0.02 ml. of concentrated CSF was then applied. In a few instances unconcentrated CSF was chromatographed by delivering 0.25–1.00 ml. of the fluid to the paper by multiple successive applications of untreated CSF. The chromatograms were run overnight, dried, and sprayed with Ninhydrin for localization of the stable carriers. Radioactivity on the strips was measured with a thin mica-window Geiger-Mueller tube and a continuously recording counting rate meter. It has previously been shown that a direct proportionality exists between the area under each peak of radioactivity and the amount of radioactivity in that area of the strip.

Zone electrophoretic analysis of concentrated CSF was conducted on Whatman No. 3 paper strips in barbital buffer at pH 8.6 for twenty-four hours at 100 volts, as previously described (17). The volume of concentrated CSF delivered was about 0.02 ml., which contained approximately 1 milligram of protein, the equivalent of 2 ml. of untreated CSF. The electrophoretic strips were counted for radioactivity in the same manner as the chromatograms described, and the proteins were then stained with bromphenol blue (16).

Identification and quantitation of iodine components

1. *Iodide.* The percentage of radioiodine as iodide in serum was estimated by planimetry of iodide areas in the radioanalysis of serum chromatograms. The percentage of radioiodine as iodide in CSF was considered equivalent to the dialyzable radioactivity, assuming negligible losses of any organic iodine compounds during analysis. This estimation was confirmed by chemical iodide analysis. It was also in agreement with values for iodide in whole CSF, derived by applying large volumes of untreated CSF directly to the chromatographic strip.

2. *Thyroid hormone.* The percentage of radioiodine as thyroxine and triiodothyronine in serum and in CSF was estimated by planimetry of areas in the radioanalysis of chromatograms.

3. *Thyroglobulin and other compounds.* The detection and quantitation of thyroglobulin discharged into serum from I^{131}-irradiated thyroid tissue, and of other organic radioiodine compounds in serum and CSF, will be discussed.

RESULTS

The ratio of total radioiodine concentration in serum compared to CSF in different patients at various times after oral administration of the isotope is indicated in Table 1. It appeared to be unrelated to the size of the dose administered. In the 5 patients included in the inorganic iodide

TABLE 2. DISTRIBUTION OF RADIOACTIVITY 48 HOURS AFTER I^{131} THERAPY

A. Iodide I^{131} in Serum and CSF

Patient	Ratio of tot. I^{131} (ser./CSF)	Per cent of total I^{131} in serum or CSF in form of*												PBI (γ/100 ml.)	
		I^-		T_4		T_3		T_G		X		Z			
		Ser.	CSF	Ser.	CSF	Ser.	CSF	Ser.	CSF	Ser.	CSF	Ser.	CSF	Ser.	CSF†
R.N. Thyroid Ca.; myxedema.	400.0	10.0	71.0	17.0	17.7	0	0	52.6	0	20.4	3.8	0	7.5	1.4	0.0036
L.L. Thyroid Ca.; myxedema.	153.0	61.5	94.5	4.5	3.5	0	0.3	27.5	0	6.5	0.7	0	1.0	1.1	0.0057
R.R. Rheum. heart dis.; euthyroid.	97.5	78.6	66	21.4	34	0	0	0	0	0	0	0	0	7.5	0.122
A.L. Graves' dis.	92.7	10.0	40	81.0	60	2	0	7	0	0	0	0	0	10.4	0.083
B.C.‡ Breast Ca.; euthyroid.	54.3	5.4	13.6	94.6	86.4	0	0	0	0	0	0	0	0	2.9	0.0674

B. Organic I^{131} in CSF

	Ratio of tot. I^{131} (ser./CSF)	Per cent of I^{131} in *dialyzed* CSF in form of						PBI (γ/100.ml.)	
		I^-	T_4	T_3	T_G	X	Z	Ser.	CSF
R.S., Thyroid Ca.; myxedema.	—	0	54.0	7.0	0	33.0	6.0	0.1	—
E.G., Thyroid Ca.; myxedema	133.0	0	60.0	5.0	0	10.0	25.0	2.5	—

* I^- = Iodide. T_4 = thyroxine. T_3 = triiodothyronine. T_G = thyroglobulin. X = compound X (Robbins). Z = unidentified material (*see* text).

† Calculated.

‡ Received a tracer dose of *l*-thyroxine.

study (samples withdrawn within eight hours after isotope administration), the serum/CSF ratios lay in the range of 44/1 to 113/1. The value of 44/1 occurred in a patient with increased intracranial pressure due to cerebral metastases and should be considered in that light. Serum/CSF iodide ratios calculated for 3 other patients at forty-eight hours after radioiodide administration ranged from 23.2/1 to 99.5/1.

When organic radioiodine was present, the serum/CSF ratios fell in the range of 50/1 to 150/1 with few exceptions. A single much higher value of 400/1 was observed in Patient R.N. This case did not differ clinically from other cases of thyroid carcinoma.

Organic compounds in CSF

Thyroxine was detected in the serum and CSF of all patients in whom organic analyses were performed.

Table 2A shows the percentage distribution of serum and CSF radioiodine in inorganic iodide and various organic iodine compounds in 5 patients.

Thyroxine accounted for 4.5 and 17.0 per cent, respectively, of the total serum radioiodine at forty-eight hours in the 2 patients with thyroid cancer who were at that time myxedematous. A euthyroid patient (R.R.) had 21.4 per cent of serum radioiodine residing in thyroxine at forty-eight hours. The value was 81 per cent in Patient A.L. with Graves' disease. The percentage of CSF radioiodine as thyroxine was in a similar range to that of serum. It constituted less than 20 per cent of total CSF radioiodine in the myxedematous thyroid cancer patients, and a higher percentage in the euthyroid and hyperthyroid patients studied.

Utilizing these percentages and the serum/CSF ratios for total radioiodine, the relative concentration of thyroxine in CSF as compared to serum was calculated:

Assuming that the specific activity of all iodine in CSF approximately equals that of serum, then

$$\frac{C'}{C} = \frac{S'}{S}, \quad \text{or} \quad \frac{C}{S} = \frac{C'}{S'}$$

where

C, S = concentration of stable iodine in CSF and serum, respectively, and

C', S' = concentration of radioactive iodine in CSF and serum, respectively.

Since there were several radioactive compounds and the ratio of only one of them is desired, correction for this must be made. Where

$T_{C'}$ = the fraction of radioactivity in CSF present as thyroxine, and

$T_{S'}$ = the fraction of radioactivity in serum present as thyroxine, then

$$\frac{C'}{S'}\cdot\frac{T_{C'}}{T_{S'}} = \frac{\text{PBI CSF}}{\text{PBI ser}}$$

or

$$\text{PBI CSF} = \frac{C'}{S'}\cdot\frac{T_{C'}}{T_{S'}}\cdot\text{PBI ser.}$$

With knowledge of the serum PBI level, a value for PBI in CSF can then be obtained. The results are indicated in Table 2A, final column. The values ranged from 0.0036 γ per 100 ml. in a patient with myxedema to 0.122 γ per 100 ml. in a euthyroid patient.

In a patient who received intravenous thyroxine and in whose serum and CSF nearly all radioactivity at forty-eight hours was still present in thyroxine, the PBI concentration in CSF was 0.0674 γ per 100 ml. (Table 2A).

Thyroxine-protein association in CSF. Contrary to reports of other workers (18), the patients with myxedema in this study showed no elevation of the CSF protein (Table 1).

The proteins of concentrated CSF, separated by zone electrophoresis in this and numerous other studies (19, 20, 21) provide a pattern similar to that of the serum proteins. A well-defined albumin and the various globulins are present in proportions more or less like those in serum. A consistent finding in this study was the presence of a small component with mobility faster than albumin, which has been reported by numerous workers (19–22).

The binding of CSF thyroxine by CSF protein is demonstrated in Figure 1. The upper portion shows a butanol-dioxane-ammonia chromatogram of CSF from a patient with Graves' disease, indicating that all the radioactivity in the dialyzed CSF is present as thyroxine. In the electrophoretic separation of this same CSF (Fig. 1, bottom) the thyroxine is separated into two peaks, one corresponding to the albumin component in the CSF protein, the other to an alpha-globulin. This pattern of thyroxine distribution, resembling qualitatively the binding of thyroxine by the proteins in serum (23), was seen also in the CSF of Patient R.R. (euthyroid), where thyroxine was similarly the sole organic iodine compound; but in the 2 patients who received intravenous radiothyroxine, the electrophoretic separation of the radioactivity differed from this example. The serum in these patients exhibited an entirely normal electrophoretic pattern for thyroxine, but in the CSF the radioactivity was bound by virtually all of the CSF proteins (Patient B.C., Fig. 2).

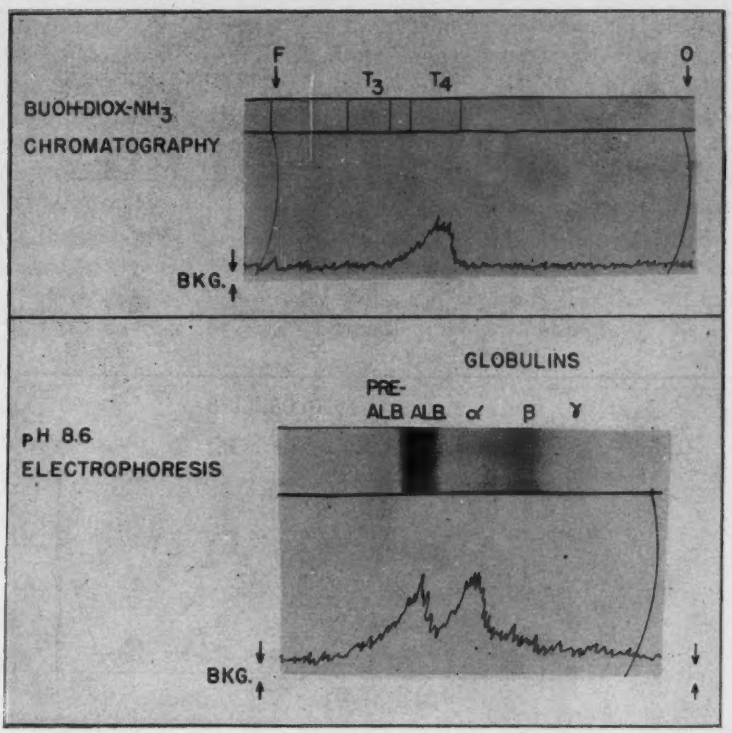

FIG. 1. Paper chromatography and electrophoresis of radioiodine in dialyzed CSF from Patient A.L. (Graves' disease), who received 20 millicuries of I^{131}. Recordings of radioactivity are mounted beneath the paper strips.

Triiodothyronine was noted in small amounts in the serum and/or CSF of 4 of the 6 patients in whom organic analyses were performed

Thyroglobulin, discharged from I^{131}-irradiated thyroid tissue, was detected as radioactivity which remained at the origin in all the chromatographic systems, and which in zone electrophoresis had a mobility between the alpha-1 and alpha-2 globulins of serum. Radioactivity fulfilling these criteria was detected in the serum of all patients who received doses of radioiodine of 50 millicuries or more. Its presence in CSF could not be demonstrated.

An iodinated compound (X), previously detected in the serum of some patients with thyroid carcinoma (24, 25), was noted in the serum of all the patients with that diagnosis included in this study. Like thyroglobulin, this substance remains at the origin in paper chromatography, but it has an electrophoretic mobility corresponding to that of serum albumin. This

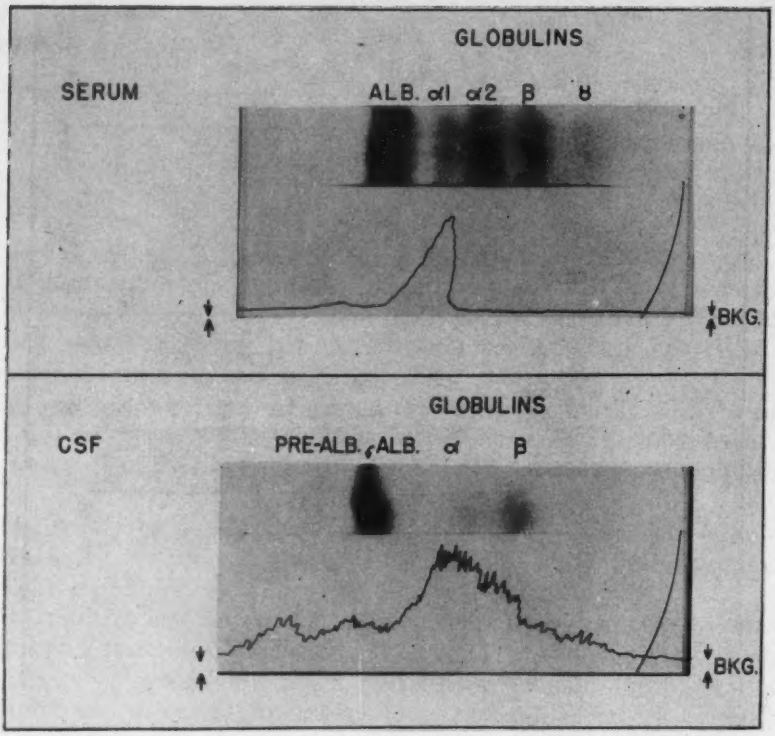

FIG. 2. Paper electrophoresis at pH 8.6 of serum and dialyzed CSF from Patient B.C. (euthyroid), who received intravenous radiothyroxine.

compound was also present in the CSF of these patients. Indeed it could be detected in concentrated CSF in most cases more easily than in the serum, where its concentration relative to thyroglobulin was often small (R.N. and L.L., Table 2A). In CSF, however, thyroglobulin was evidently not present, and virtually all of the radioactivity remaining at the origin in chromatography could be accounted for in the CSF albumin fraction by electrophoresis, and was thus attributable to this thyroid cancer compound.

An *additional unknown substance* was detected in the concentrated CSF of thyroid cancer patients who received radioiodine doses greater than 100 millicuries. It was not noted in the serum of these patients. This compound had an Rf in butanol-dioxane-ammonia chromatograms of 0.08 to 0.09, which is like that of mono- and diiodotyrosine. In collidine-water the Rf was 0.53, just in advance of mono-iodotyrosine; but in butanol-acetic acid, the substance moved well beyond the iodinated tyrosines, and was poorly

separable from the broad peak of thyroxine which was also present. The actual Rf for this compound in butanol-acetic-acid, detected by a two-dimensional technique (electrophoresis and chromatography) was 0.87. Binding of this compound to CSF proteins, as shown by electrophoresis, is not certain; in the 4 patients in whom it was detected, no consistent pattern was evident, but elution of electrophoretic strips in butanol-acetic acid chromatography suggested that its mobility is like that of the CSF "pre-albumin" (Fig. 4). To characterize this CSF compound further, the portion of a butanol-dioxane-ammonia chromatogram (from Patient L.L.) which contained the unidentified radioactivity in question was cut out and attached as the origin of an ascending chromatogram, in a system

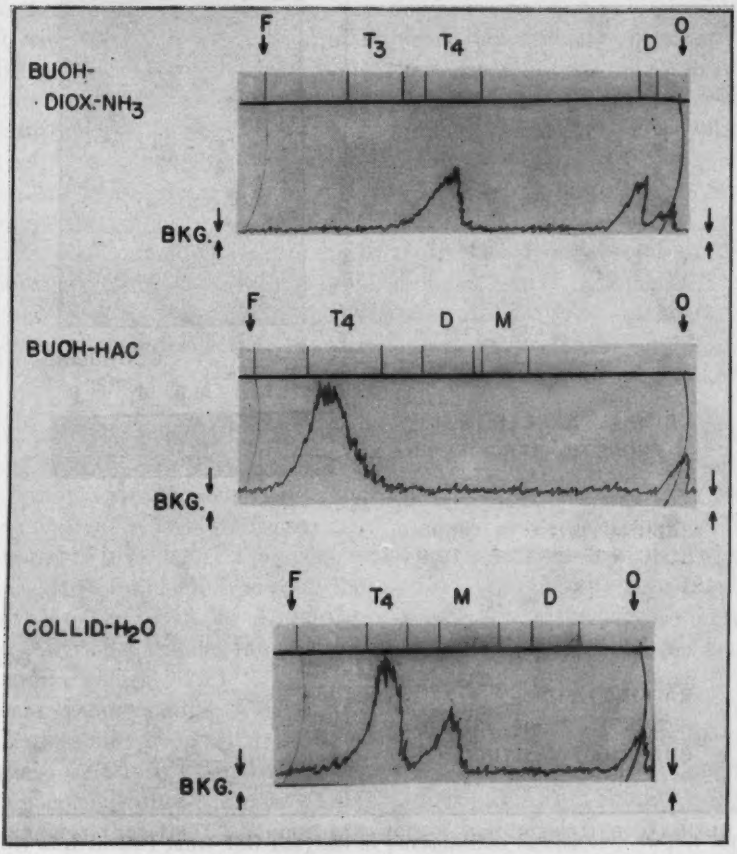

FIG. 3. Paper chromatography in three solvent systems of dialyzed CSF from Patient E.G. (thyroid carcinoma), who received 125 millicuries of I^{131}.

consisting of ether, glacial acetic acid, and water; 150:30:5. All of the radioactivity in this chromatogram advanced to a single peak at the solvent front.

With Patient L.L., further analyses were performed in order to define more conclusively certain features of the CSF organic iodine content. The

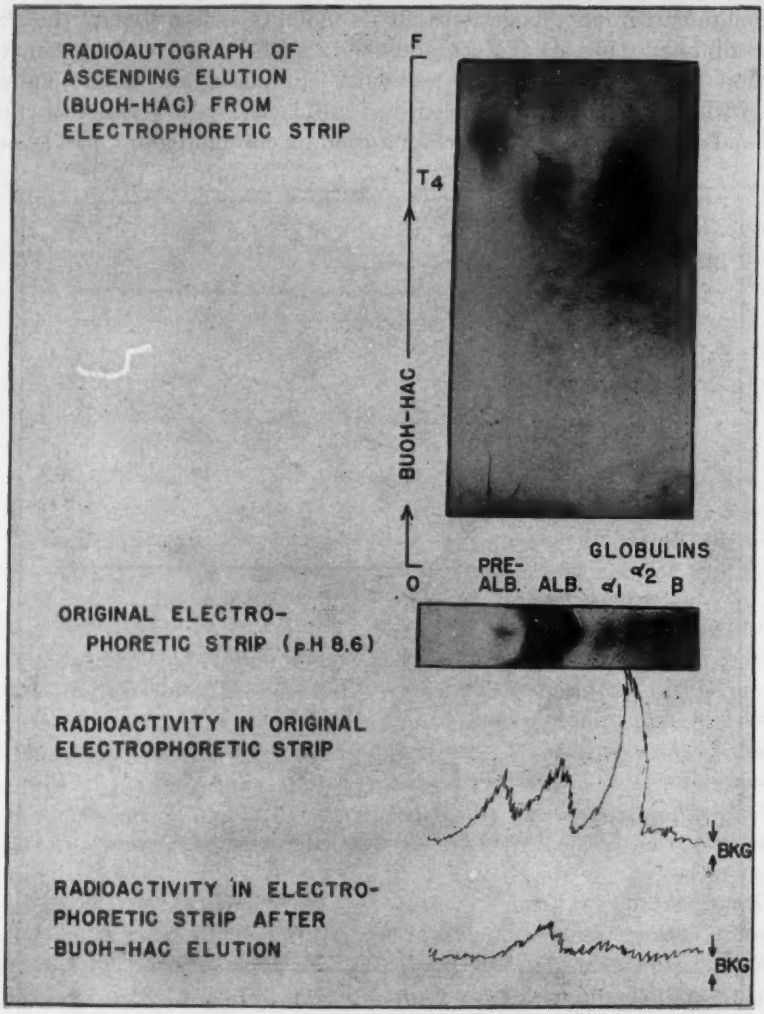

FIG. 4. Two-dimensional radioanalysis of dialyzed CSF from Patient L.L. (thyroid carcinoma), who received 200 millicuries of I^{131}. The electrophoretic strip was eluted in BuOH-HAc; the resulting chromatogram is mounted above the strip.

CSF of this patient exhibited four radioactive compounds by chromatography. The patterns resembled those of Patient E.G. (Fig. 3; Table 2B). Thyroxine and triiodothyronine constituted 68 per cent of the organic radioiodine activity; compound X accounted for 13 per cent; and the unidentified substance (Z), 19 per cent. The electrophoretic pattern of this same CSF (Fig. 4, middle) showed three peaks, corresponding to pre-albumin, albumin, and inter-alpha globulin. The upper portion of Figure 4 is the radioautograph of the activity which was eluted upward from the electrophoretic strip, when it was utilized as the origin of an ascending chromatogram in the butanol-acetic acid system. Radioactivity with the Rf of thyroxine has ascended from the alpha-globulin region; a smaller amount with similar Rf has ascended from the albumin component; and from the pre-albumin, activity has ascended to a position just beyond that of thyroxine. The lower portion of Figure 4 indicates the distribution of radioactivity which remained in the same electrophoretic strip after the elution. Considerable radioactivity was removed from all the components. (In addition, 40 per cent was lost due to radioactive decay). In the albumin portion, significant radioactivity remained, which presumably corresponded to compound X. Nearly all of the radioactivity in the alpha-globulin portion was removed with the elution of thyroxine. If radioactivity had remained in this position, it would correspond to thyroglobulin, which has an electrophoretic mobility like that of the thyroxine-binding protein. These data and similar considerations in the cases of E.G. and R.N. indicate that thyroglobulin is not present in CSF.

DISCUSSION

The presence in CSF of very low concentrations of iodine in several forms is confirmed in these investigations. The values reported here are generally lower than those reported by other workers. For example, CSF iodide concentration in this study averaged 1.35 per cent of the serum value compared to a value of 12 per cent found by Greenberg and his co-workers in dogs (10). Similarly, for total iodine, CSF concentrations in these patients were 0.26 to 2.3 per cent of those in serum; whereas Gildea and Man, in 8 euthyroid patients, found values ranging from 1.6 to 4.5 per cent of the serum values.

Because only a single CSF sample was procured from each patient it was impossible to construct a time curve for the entry of radioiodine or its various forms into CSF. In the values for the serum/CSF iodide ratio, there is considerable variation (Table 1, final column). The data might at first suggest that the CSF concentration of iodide relative to serum was still increasing at four hours after radioiodine administration, but this is controverted by the values for M.D. at eight hours (serum/CSF = 113.0),

and L.L. at forty-eight hours (serum/CSF = 99.5). It is probable that a steady state for iodide is achieved within two hours after radioiodine administration, and that the data reflect a rather wide individual variation in the relative concentration of iodide in serum and CSF. The work of Greenberg (10) and others indicates that the relative ease of entry of the various halides into CSF is in the inverse order of their ionic diameters. It is unlikely, however, that the ready passage of iodide across the blood-brain barrier is prevented primarily by its larger ionic size. If it is assumed that larger molecules such as proteins enter CSF by transudation from serum (and the major spectrum of CSF protein resembles that of serum), then it may also be assumed that the iodide ion is not excluded from CSF on the basis of its size. The very low concentration of iodide in CSF supports the argument that diffusion alone cannot account for the composition of CSF, but that energy is expended, either in the selective secretion of certain substances into CSF, or in the maintenance of a concentration gradient.

The derived values for PBI concentration in CSF (Table 2A, final column) were lowest in myxedema. The value for the patient with Graves' disease (0.083 γ per 100 ml.) was only moderately higher than that for a clinically euthyroid patient who received labeled thyroxine (0.067 γ per 100 ml.). It is surprising that the highest value (0.122 γ per 100 ml.) occurred in a euthyroid patient. In general, however, comparison between levels of serum PBI and CSF-PBI indicates a reasonably constant relationship, and suggests that CSF levels of thyroxine are a reflection of serum levels.

It is not understood why, in a euthyroid patient (R.R.) and in one who was hyperthyroid (A.L.), thyroxine in CSF was bound primarily by inter-alpha globulin (presumably the same as the thyroxine-binding protein of serum) and by albumin; whereas in the euthyroid patients (B.C. and M.W.) intravenously injected radiothyroxine was bound by virtually all the CSF proteins.

The serum alpha-globulin that specifically binds thyroxine seems to be present in CSF. Its actual concentration in either fluid is too small to be estimated by present techniques. Whereas thyroxine concentration in CSF is 1 to 2 per cent that of serum, protein concentration in CSF is less than 0.5 per cent the serum value. If it can be assumed that the specific thyroxine-binding protein constitutes a roughly similar fraction of the protein in both fluids, then in CSF a given quantity of thyroxine is provided only one quarter as much specific protein for binding as it is in serum. It may be that in certain patients (*e.g.*, B.C., and M.W.), for reasons not understood, the relative concentration of thyroxine-binding protein in CSF is even lower than estimated by these calculations. This

would result in a considerable degree of nonspecific binding, even for low values of CSF thyroxine.

The data in Patient B.C. (Fig. 2) suggest that thyroxine can enter CSF, at least in part, independent of serum protein, since in CSF thyroxine exists in association with protein components that do not bind it in serum, including at least one (pre-albumin) which is not even present in serum.

The results indicate that compound X can penetrate the blood-brain barrier, whereas thyroglobulin discharged from I^{131}-irradiated thyroid tissue cannot. This can be understood in terms of the relative size of these compounds. The former substance, according to sedimentation studies in the ultracentrifuge (26), has a molecular weight of about 60,000, and could be secreted by the cells of the choroid plexus in the same way that serum proteins are presumably secreted. Thyroglobulin, on the other hand, is in a size-class (M.W. 650,000) (26, 27) much larger than that of the serum proteins, and may well encounter difficulty in transfer on this basis.

The new iodinated substance (Z) detected in chromatograms of CSF in the present study remains unidentified. Its behavior in the chromatographic systems studied does not correspond to that of the amino acids ordinarily found in thyroid tissue or in biologic fluids. Glucuronic-acid and acetic-acid derivatives of the thyroid hormone may be excluded on the basis of their Rf's in certain solvent systems (28, 29), as may the alpha-keto forms of thyroxine and triiodothyronine (30). Thyroxamine has been similarly excluded. Its Rf in the butanol-acetic acid system, detected by the diazotized sulfanilamide method (31), is 0.87, which would be compatible with that of the unidentified substance. In the butanol-dioxane-ammonia system, however, the Rf of thyroxamine is 0.91, whereas that of the unidentified substance is 0.08–0.09.

The origin of substance Z is not clear. It was noted in each of 4 patients, all with thyroid cancer, all myxedematous at the time of the treatment, and all treated with radioiodine doses larger than 100 millicuries. Because it was not detected in serum it is presumably produced within the central nervous system. Moreover, its absence from the serum of these patients suggests that it is not a characteristic product of irradiated thyroid cancer tissue, particularly since central nervous system metastases were not present. If the material is a central nervous system metabolite of thyroid hormone it should be detectable in the CSF of all patients, although the possibility exists that only in those who received the larger doses of radioiodine was the activity adequate to permit detection by the present methods. On the other hand, the absence of this material in the CSF of Patients B.C. and M.W., who received intravenous radiothyroxine,

militates against this likelihood. A third possibility, still unexplored, is that the substance is produced by the central nervous system in profound myxedema.

SUMMARY

1. Iodine compounds in cerebrospinal fluid (CSF) were studied in 11 patients who received therapeutic doses of radioiodine, and in 2 patients who received tracer doses of radioactive thyroxine.

2. CSF iodide concentration in 8 patients ranged from 0.9 to 4.3 per cent of serum values, with an average of 1.3 per cent.

3. Thyroxine was detected in the CSF of all patients in whom organic analyses were performed. The average concentration in 5 patients was 1.1 per cent of serum values. Calculated values for the concentration of protein-bound iodine in CSF ranged from 0.004 microgram per 100 ml. in a patient with myxedema to 0.122 microgram per 100 ml. in a euthyroid subject. In a patient who received intravenous radiothyroxine, the value was 0.067 microgram per 100 ml. The specific alpha-globulin that binds thyroxine in serum seems to be present in CSF in low concentration. Small amounts of triiodothyronine were detected in the CSF of 3 patients.

4. Thyroglobulin discharged from I^{131}-irradiated thyroid tissue was not detected in the CSF of any patients.

5. In the CSF of 4 patients with thyroid carcinoma the presence of a compound, (X), which is associated with certain cases of thyroid cancer, was demonstrated. An unidentified substance, (Z), was also detected in the CSF of these patients. Its behavior in three chromatographic systems was unlike that of the commonly observed iodinated amino acids or the metabolites of thyroid hormone.

Acknowledgments

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REFERENCES

1. Asher, R.: Myxoedematous madness, *Brit. M. J.* **2**: 555–562, 1949.
2. Dunlap, H. F., and Moersch, F. P.: Psychic manifestations associated with hyperthyroidism, *Am. J. Psychiat.* **91**: 1215–1238, 1935.
3. Jameison, G. R., and Wall, J. H.: Psychoses associated with hyperthyroidism, *Psychiatric Quart.* **10**: 464–480, 1936.
4. Sensenbach, W.; Madison, L.; Eisenberg, S., and Ochs, L.: The cerebral circulation and metabolism in hyperthyroidism and myxedema, *J. Clin. Invest.* **33**: 1434–1440, 1954.
5. Scheinberg, P.; Stead, F. A., Jr.; Brannon, E. S., and Warren, J. V.: Correlative

observations on cerebral metabolism and cardiac output in myxedema, *J. Clin. Invest.* **29**: 1139–1146, 1950.

6. Sokoloff, L.; Wechsler, R. L.; Mangold, R.; Balls, K., and Kety, S. S.: Cerebral blood flow and oxygen consumption in hyperthyroidism before and after treatment, *J. Clin. Invest.* **32**: 202–208, 1953.
7. Scheinberg, P.: Cerebral circulation and metabolism in hyperthyroidism, *J. Clin. Invest.* **29**: 1010–1013, 1950.
8. Condon, J. V.; Becka, D. R., and Gibbs, F. A.: Electroencephalographic abnormalities in hyperthyroidism, *J. Clin. Endocrinol. & Metab.* **14**: 1511–1518, 1954.
9. Gildea, E. F., and Man, E. B.: Distribution of iodine in blood serum and in cerebrospinal fluid, *Arch. Neurol. & Psychiat.* **49**: 93–97, 1943.
10. Greenberg, D. M.; Aird, R. B.; Boelter, M. D. D.; Campbell, W. W.; Cohn, W. E., and Murayama, M. M.: A study with radioactive isotopes of the permeability of the blood-cerebrospinal fluid barrier to ions, *Am. J. Physiol.* **140**: 47–64, 1943.
11. Gross, J., and Leblond, C. P.: Metabolism of the thyroid hormone in the rat as shown by physiological doses of labeled thyroxine, *J. Biol. Chem.* **184**: 489–500, 1950.
12. Johnson, H. W., and Albert, A.: The excretion and distribution of I^{131} following administration of physiologic amounts of labeled iodide, diiodotyrosine and thyroxine in the rat, *Endocrinology* **48**: 669–681, 1951.
13. VanArsdel, P.; Hogness, J. R.; Williams, R. H., and Elgee, N.: Comparative distribution and fate of I^{131}-labeled thyroxine and triiodothyronine, *Endocrinology* **55**: 332–343, 1954.
14. Barker, S. B.: Determination of protein-bound iodine, *J. Biol. Chem.* **173**: 715–724, 1948.
15. Nesh, F., and Peacock, W. C.: Use of radioactive iodine in microdetermination of protein-bound blood iodine, *Analyt. Chem.* **22**: 1573, 1950.
16. Robbins, J., and Rall, J. E.: Zone electrophoresis in filter paper of serum I^{131} after radioiodide administration, *Proc. Soc. Exper. Biol. & Med.* **81**: 530–536, 1952.
17. Alpers, J. B.; Robbins, J., and Rall, J. E.: The hydrolysis of rat thyroglobulin by thyroidal enzymes, *Endocrinology* **56**: 110–119, 1955.
18. Thompson, W. O.; Thompson, P. K.; Silveus, E., and Dailey, M. E.: The cerebrospinal fluid in myxedema, *Arch. Int. Med.* **44**: 368–373, 1929.
19. Buecher, T.; Matzelt, D., and Pette, D.: Papierelektrophorese von Liquor cerebrospinalis, *Klin. Wchnschr.* **30**: 325–330, 1952.
20. Esser, V.: Die elektrophoretische Untersuchung der Liquoreiweisskoerper und ihre klinische Bedeutung, *München. med. Wchnschr.* 94: 2313–2318, 1952.
21. Mies, H. J.: Einengung von Liquor cerebrospinalis als Vorbereitung zur Papierelektrophorese, *Klin. Wchnschr.* **31**: 159–161, 1953.
22. Fisk, A. A.; Chanutin, A., and Klingman, W. O.: Observations on a rapidly migrating electrophoretic component of cerebrospinal fluid, *Proc. Soc. Exper. Biol. & Med.* **78**: 1–3, 1951.
23. Robbins, J., and Rall, J. E.: Thyroxine-binding capacity of serum in normal man, *J. Clin. Invest.* (in press).
24. Robbins, J.; Rall, J. E., and Rawson, R. W.: A unique serum iodine component in certain patients with thyroid carcinoma, (abstract) *J. Clin. Endocrinol. & Metab.* **13**: 852–853, 1953.
25. Robbins, J.; Rall, J. E., and Rawson, R. W.: A new serum iodine component in

patients with functional carcinoma of the thyroid, *J. Clin. Endocrinol. & Metab.* **15**: 1315–1331, 1955.

26. ROBBINS, J.; PETERMANN, M. L., and RALL, J. E.: Thyroglobulin in serum after I^{131} therapy. II. Sedimentation in the ultracentrifuge, *J. Biol. Chem.* **208**: 387–393, 1954.
27. HEIDELBERGER, M., and PEDERSON, K. O.: The molecular weight and isoelectric point of thyroglobulin, *J. Gen. Physiol.* **19**: 95–108, 1935.
28. TAUROG, A.; BRIGGS, F. N., and CHAIKOFF, I. L.: I^{131}-labeled *l*-thyroxine. II. Nature of the excretion product in bile, *J. Biol. Chem.* **194**: 655–668, 1952.
29. PITT-RIVERS, R.: Personal communication.
30. ROCHE, J.; MICHEL, O.; MICHEL, R., and TATA, J.: On the products of hepatic and renal elimination of thyroxine and triiodothyronine labeled with iodine-I^{131}. Harwell 2nd Radioisotope Technical Conference. New York and London, Oxford University Press, 1954, vol. 1, pp. 325–329.
31. BLOCK, R. J.; DURRUM, E. H., and ZWEIG, G.: A Manual of Paper Chromatography and Paper Electrophoresis. New York, Academic Press Inc., 1955, p. 95.

THE INFLUENCE OF THE THYROID ON ADRENOCORTICAL FUNCTION*†

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THE results of several clinical and experimental studies using radioactive iodine are in agreement that corticotropin and cortisone inhibit the production of thyroid hormone, although the mechanism of this inhibition is still in dispute (1, 2, 3). However, information concerning the influence of thyroid hormones on adrenocortical activity is conflicting. Evaluations of adrenocortical function in clinical hyperthyroidism, based on anatomic findings, have yielded contradictory reports. Marine (4) and LeCompte (5) reported a decrease in adrenal size in hyperthyroid patients. Holst (6) found adrenal hyperplasia in a few such patients, and Means (7) found no remarkable change in the adrenals. Measurements of urinary steroid excretion have shown normal or low 17-ketosteroids (8–11) and low formaldehydogenic steroids (12) in hyperthyroidism. Plasma 17-hydroxycorticosteroid levels in a few hyperthyroid patients have been in the normal range (13).

In clinical myxedema the urinary excretions of 17-ketosteroids and 17-hydroxycorticosteroids are also frequently low (8–12, 14).

In contrast to the clinical observations, hyperthyroidism which has been experimentally induced in animals by feeding thyroid powder seems to increase adrenocortical activity, as judged by several criteria. In guinea pigs, thyroid feeding has resulted in a 25 per cent increase in adrenal size (15). Rat adrenals also increase in size when thyroid is given by mouth (16). Deane and Greep (17) noted an increase in the zona fasciculata in thyroid-fed rats, and by cytochemical techniques demonstrated in this zone an increase in certain cytochemical staining reactions believed to be

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indicative of steroids possessing active ketone groups. A decrease in this staining reaction occurs in the adrenals of hypothyroid rats.

A decrease in adrenal size occurs in rats which have been thyroidectomized or fed thiouracil (17–20). A decreased tolerance of hypothyroid rats to cold has also been interpreted as an impairment of adrenal function (20).

A consideration of the previous work in this field reveals that there are few quantitative data concerning the requirements for, or the utilization of adrenocortical steroids under conditions of increased or decreased thyroid activity. Moreover, it is apparent that a real conflict exists between the reported response of the adrenal cortex in clinical hyperthyroidism and the hyperthyroidism induced by thyroid feeding in experimental animals.

In order to attempt to answer some of these questions, combined clinical and experimental studies have been carried out in patients with thyroid disease and in guinea pigs with induced hyperthyroidism.

METHODS

Infusion of hydrocortisone in patients

Hydrocortisone in a dose of 15 mg. per square meter of body surface was administered intravenously in 1,000 ml. of 5 per cent glucose in water at a constant rate, over a four-hour period to control, hyperthyroid and myxedematous patients. The diagnoses of hyperthyroidism and myxedema were well established, as judged from both clinical manifestations and laboratory data. Hospitalized nonendocrine patients in good general condition served as the controls. The intravenous infusions were started at 8:00 A.M., with the patients in the fasting state. At the end of the infusion and before the last sample was drawn, they were allowed lunch. Blood samples were drawn in heparinized syringes at the start of the infusion, after one hour, at the end of the infusion, and two hours later.

In most patients urine was collected quantitatively on the day prior to, and on the day of the hydrocortisone infusion, for measurements of urinary 17-OH corticosteroids by the method of Silber and Porter (21).

Experimental hyperthyroidism in guinea pigs

Guinea pigs were chosen for these experiments because they excrete relatively large amounts of free 17-hydroxycorticosteroids. Male animals weighing approximately 250 Gm. were housed in individual metabolic cages and fed Purina Rabbit Chow ad libitum. Ascorbic acid was injected subcutaneously in a dosage of 10 mg. twice a week. Urine was collected for 24-hour periods through a coarse brass screen, in order to exclude feces and food particles. The urine from 3 guinea pigs collected for 24-hour periods was pooled for steroid analysis. The animals were weighed at frequent intervals. After a control period of ten days they were given a daily subcutaneous injection of 0.2 mg. of *l*-thyroxine for nine days. They were observed for an additional twelve days during recovery from the hyperthyroid state.

The effect of different doses of *l*-thyroxine was observed in a second series of guinea pigs. After several control days during which they were injected with physiologic sodium chloride solution, they were given a daily subcutaneous injection of 0.025 mg. of *l*-thyroxine for seven to ten days, after which the dosage was increased to 0.05 mg. In 1

guinea pig this dosage was subsequently increased to 0.10 mg. a day. The animals were weighed daily and metabolic rates were measured each morning.

The apparatus for determining the metabolic rate is pictured in Figure 1. The animal was placed in a wide-mouth jar together with a container of soda lime to absorb carbon dioxide and moisture. The opening of the jar was closed by a tight fitting rubber cork with three openings. One opening was for a thermometer for recording temperature, the second for oxygen intake, and the third for a firm-walled tube leading to a 100-cc. buret inverted in a column of water for recording oxygen consumption. After placing the animal in the jar it was flushed with oxygen for ten minutes and the oxygen inlet clamped

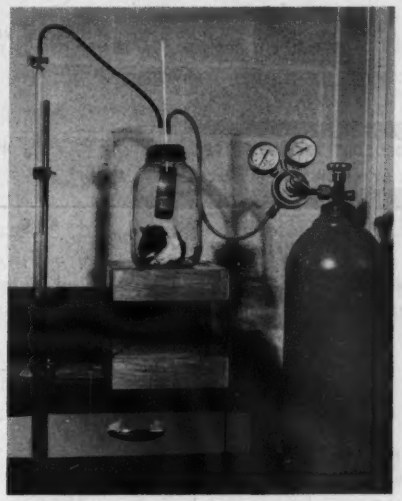

FIG. 1. Apparatus for determination of metabolic rates of small laboratory animals.

off. The volume of oxygen consumed was then measured in cubic centimeters by noting the rise of fluid in the buret. A constant oxygen tension was maintained in the jar by lowering the buret into the column of water at the same rate at which the oxygen was being used. Oxygen consumption was measured for a five-minute period and the volume corrected for temperature and barometric pressure.

Determination of 17-hydroxycorticosteroids

Plasma 17-hydroxycorticosteroids (hereafter referred to as 17-OH-CS) were measured by a modification of the method of Nelson and Samuels (22). Measurements of 17-OH-CS in human urine were made after β-glucuronidase hydrolysis and chromatography on a Florisil column.

The 17-OH-CS content of guinea-pig urine was measured by the method of Silber and Porter (21); β-glucuronidase hydrolysis was not used, as the guinea pig has been found to excrete 17-OH-CS almost exclusively in the free form (23).

RESULTS

Disappearance of infused hydrocortisone from the blood of patients with thyroid disease

The rates of disappearance of intravenously administered hydrocortisone from the blood plasma of normal, hyperthyroid and myxedematous pa-

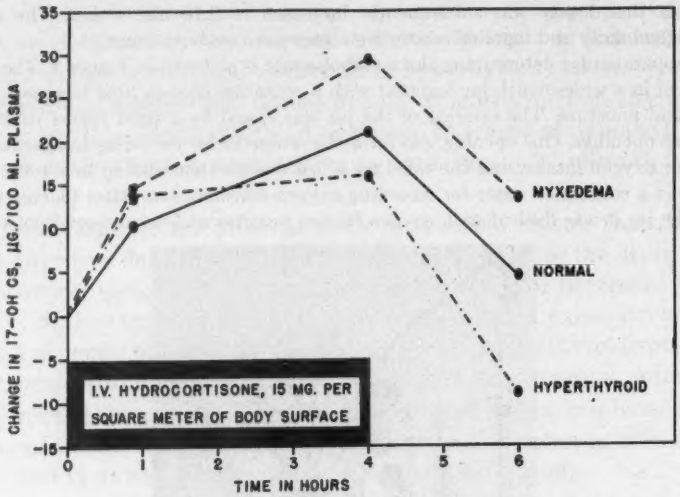

FIG. 2. Disappearance of intravenously administered hydrocortisone from the blood of normal, myxedematous and hyperthyroid patients.

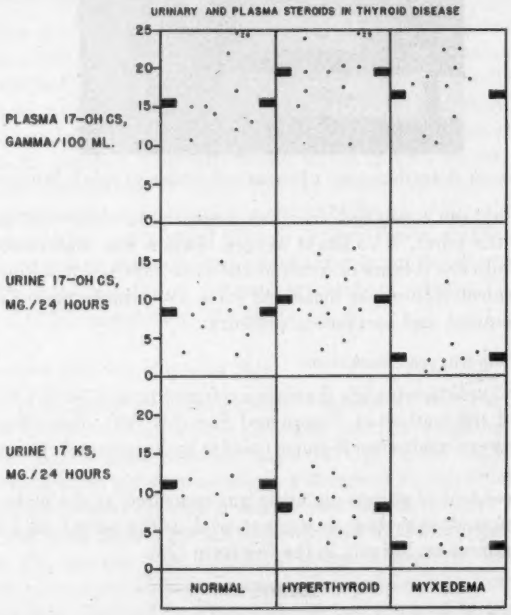

FIG. 3. Urinary 17-KS, 17-OH-CS, and plasma 17-OH-CS in normal, hyperthyroid and myxedematous patients.

tients are illustrated in Figure 2. The initial plasma level of steroid for each group was adjusted to zero on the curves and the rise from the initial level was plotted to permit a comparison of the three groups. The initial average value in the control group was 16.5 μg. per 100 ml. (range, 10–28 μg.); in hyperthyroidism, 19 μg. (range, 10–29 μg.); and in myxedema, 17.6 μg. (range 11–23 μg.). These plasma 17-OH-CS values are shown in Figure 3. Each curve represents the average values from 8 patients.

A comparison of these results indicates a difference in the rate of degradation of hydrocortisone in the three groups. This difference is manifested throughout the infusion period and is most evident two hours after the end of the infusion. The rate of hormone disappearance in the myxedematous patients was slower than in the controls, whereas that in the hyperthyroid group was more rapid. At six hours, the actual average plasma level of steroid was 31.5 μg. per 100 ml. in the myxedematous patients, 19.5 μg. in the controls, and 11.1 μg. in the hyperthyroid group. A statistical analysis of these figures revealed a P value of less than .02 between normal and myxedematous patients. The P value between normal and hyperthyroid patients was less than .001, and between myxedematous and hyperthyroid patients also less than .001. A simple calculation from these data showed that, two hours after the infusion, the myxedematous patients had over 2,000 μg. more hydrocortisone in the blood and extracellular fluid alone, than did the hyperthyroid patients.

Urinary 17-OH-CS before and during i.v. hydrocortisone

In order to learn if these changes in plasma steroid levels might be accounted for by differences in the rate of urinary excretion, a comparison was made of the 17-OH-CS excreted on the day prior to the infusion and in the 24-hour period in which the infusion was given (Fig. 4). Prior to the hydrocortisone infusion the average 24-hour urinary excretion of 17-OH-CS by the controls was 8.7 mg. (range, 3.9–14.8 mg.); by the hyperthyroid patients, 10.1 mg. (range, 4.7–16.8 mg.); and by the myxedematous patients, 3 mg. (range, 0.37–12.10 mg.). On the day of the infusion the average 24-hour excretion of 17-OH-CS by the controls was 14.1 mg. (range, 6.0–15.4 mg.); by the hyperthyroid patients, 12.2 mg. (range, 5.8–24.6 mg.); and by the myxedematous patients, 8.1 mg. (range, 5.9–12.1 mg.). From these data it may be seen that the hyperthyroid patients excreted a lesser increment of 17-OH-CS (2.1 mg.) on the day of the infusion than did the control patients, who excreted an increase of 5.4 mg. The more rapid disappearance of hydrocortisone from the plasma in hyperthyroidism cannot, therefore, be attributed to an increase in urinary excretion but must represent increased degradation.

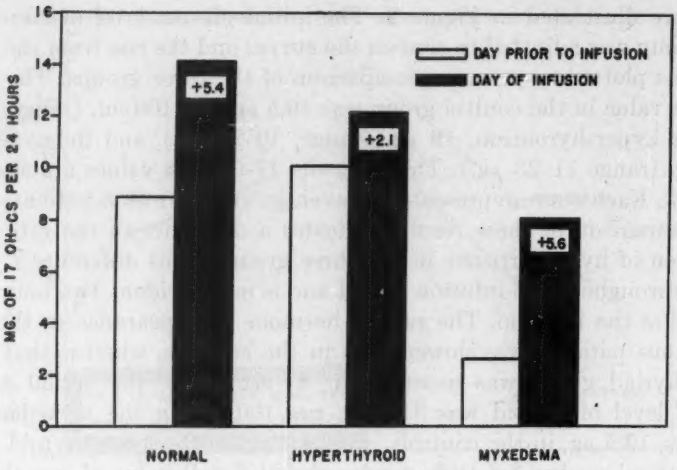

FIG. 4. Comparison of urinary 17-OH-CS on the day prior to, and on the day of the hydrocortisone infusion.

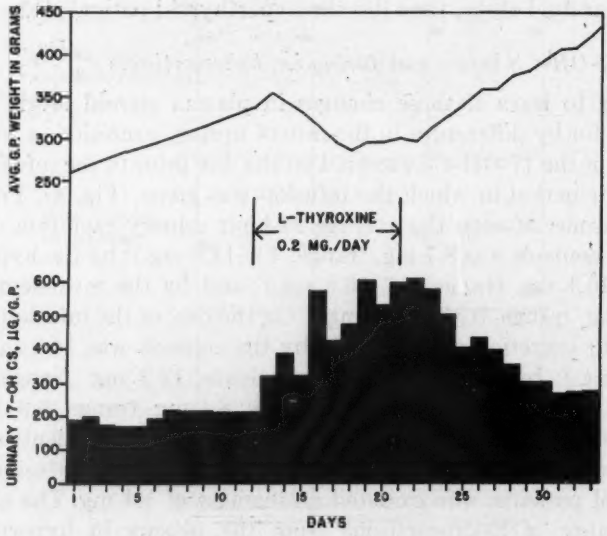

FIG. 5. Effects of *l*-thyroxine subcutaneously on weight and 17-OH-CS excretion of guinea pigs.

17-OH-CS excretion by guinea pigs with induced hyperthyroidism

During the control period the first group of guinea pigs excreted an average of 150–225 μg. of 17-OH-CS per day. When *l*-thyroxine in a dose of 0.2 mg. a day was administered subcutaneously, there was a decrease in body weight and a rapid increase in urinary 17-OH-CS to 600 μg. per day per guinea pig (Fig. 5). This increased adrenocortical activity persisted for several days after the cessation of the thyroxine.

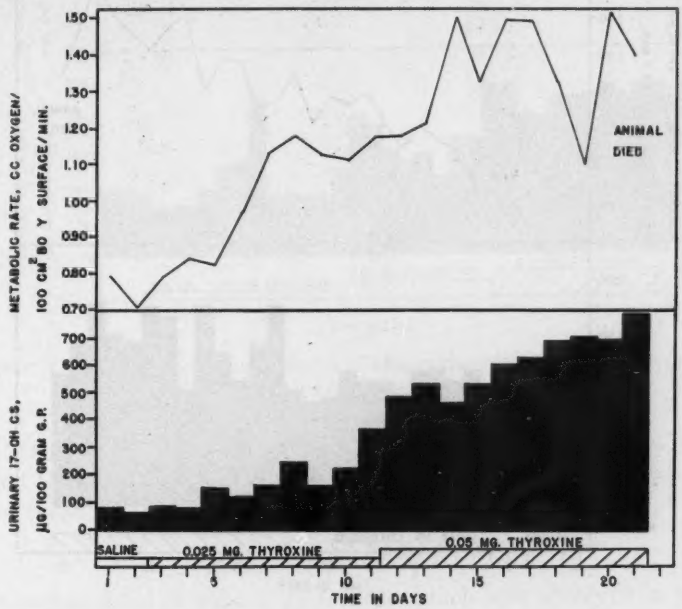

FIG. 6. Effects of increasing dosages of *l*-thyroxine subcutaneously on the metabolic rate and urinary 17-OH-CS excretion of guinea pigs.

Smaller and gradually increasing doses were administered to a second group of guinea pigs. In the first animal receiving 0.025 mg. of thyroxine a day (Fig. 6) there was a rapid rise in urinary 17-OH-CS excretion (expressed as micrograms of 17-OH-CS per 100 grams of body weight per day) from 80 to 360 μg. There was an associated increase in the metabolic rate (expressed as cubic centimeters of oxygen consumed per 100 square centimeters of body surface per minute). With the increase in metabolism, the animal ceased to gain weight. When the thyroxine was increased to 0.05 mg. a day, the metabolic rate again increased, the steroid output rose to 750 μg. and the animal died after twelve days on this dose of thyroxine.

In a second animal (Fig. 7), the subcutaneous injection of 0.025 mg. of thyroxine a day resulted in a rise in steroid output which became maximal within forty-eight hours and preceded by six days the maximal elevation of the metabolic rate. Increasing the dosage of thyroxine to 0.05 mg. caused further increases in adrenocortical activity and in the metabolic rate, with death of the animal in eleven days.

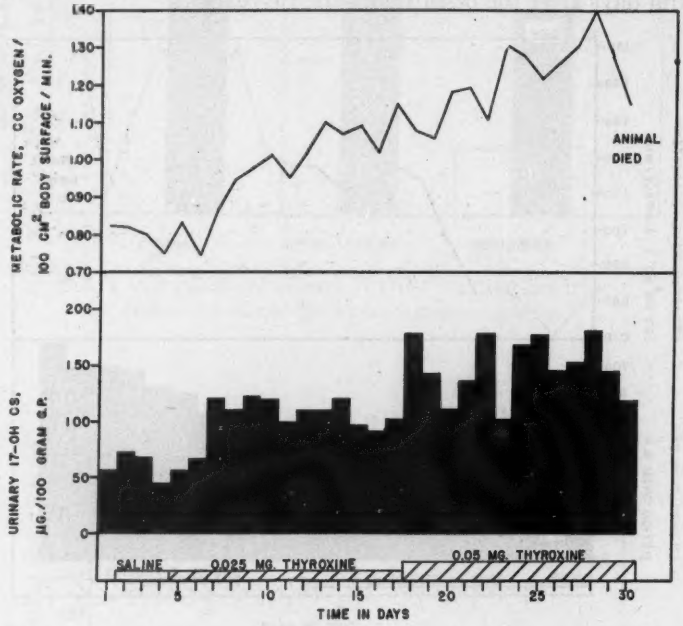

FIG. 7. Effects of increasing dosages of *l*-thyroxine subcutaneously on the metabolic rate and urinary 17-OH-CS excretion of guinea pigs.

In a third animal (Fig. 8), a similar rise in 17-OH-CS excretion occurred within one day after starting thyroxine. This rise in steroid output preceded by three days a significant rise in the metabolic rate. Further increase in thyroxine dosage resulted in maximal increases in steroid output prior to the maximal rise in the metabolic rate for that particular thyroid dose. On the lower dosages of 0.025 and 0.05 mg. of thyroxine there was a tendency for this animal's steroid output to return toward normal levels after an initial rise. The fall in urinary steroid was coincident with the increases in metabolic rate. This effect was also noted in a recent observation on another guinea pig.

As indicated by the findings in the first guinea pig, an occasional animal

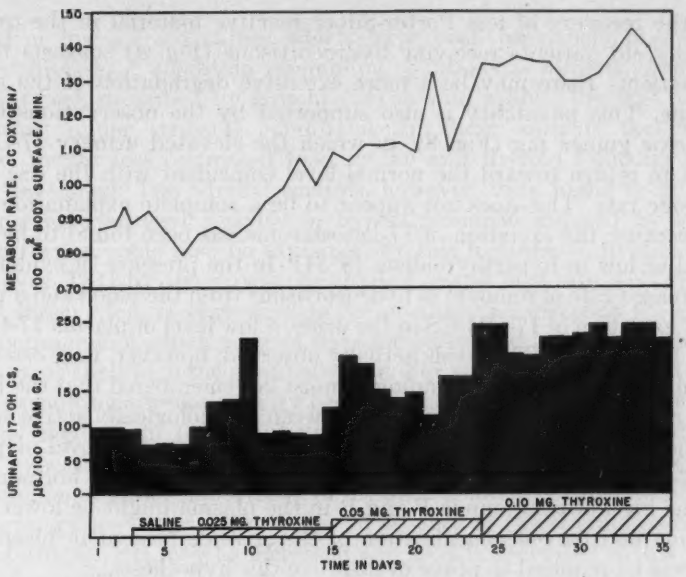

FIG. 8. Effects of increasing dosages of *l*-thyroxine subcutaneously on the metabolic rate and urinary 17-OH-CS excretion of guinea pigs.

exhibited a marked adrenocortical response to thyroxine. This was attributed to individual differences in the genetically heterogeneous animals used in these studies.

DISCUSSION

The normal level of plasma 17-OH-CS which was observed in patients with myxedema seems inconsistent with the low urinary excretion of 17-OH-CS (Fig. 3). This may be due to a decreased rate of steroid degradation, whereby the adrenal would be required to secrete less steroid to maintain a normal plasma level. The possibility was considered that, in myxedema, the normal plasma level of 17-OH-CS in the face of low urinary excretion might be due to an increased binding of the steroid by the plasma proteins. When the plasma of patients with myxedema was dialyzed against buffer containing hydrocortisone, the binding of the steroid proved to be no greater than in the plasma of euthyroid patients.

Several mechanisms have been considered in an attempt to explain the lack of consistent evidence of adrenocortical hyperactivity in clinical hyperthyroidism compared to the increased adrenal activity noted follow-thyroid administration to laboratory animals.

One such mechanism would be an altered pathway of steroid degradation.

Thus the recovery of less Porter-Silber reactive material in the urine of hyperthyroid patients receiving hydrocortisone (Fig. 4) suggests that in such patients there may be a more extensive degradation of the steroid molecule. This possibility is also supported by the observations on the thyrotoxic guinea pig (Fig. 8), in which the elevated urinary 17-OH-CS tended to return toward the normal level coincident with the rise in the metabolic rate. This does not appear to be a complete explanation, however, because the excretion of 17-ketosteroids has been found to be below normal or low in hyperthyroidism (8–11). In the presence of evidence for an increased rate of removal of hydrocortisone from the blood and a normal rate of excretion of 17-OH-CS in the urine, a low level of plasma 17-OH-CS would be expected. The levels actually observed, however, were essentially normal. In considering this finding, it must be remembered that the Porter-Silber reaction does not distinguish between physiologically active steroids and their degradative products. In hyperthyroidism the level of plasma free 17-OH-CS may not be a totally reliable index of active hormone, and the true level of compounds F and B in the plasma might be lower. Fractionation and partial identification of the steroids present in plasma and urine will be required to prove or disprove this hypothesis.

A species difference in response would be a second explanation for the inconsistency between spontaneous and induced hyperthyroidism. Beierwaltes (8) was unable to increase the excretion of 17-ketosteroids in myxedematous patients above normal levels by the administration of up to 1.0 mg. of *l*-thyroxine. Further studies, using measurements of 17-OH-CS, are needed to determine whether or not this is a valid explanation.

Thirdly, the duration and intensity of the hyperthyroid state may be an important factor in determining the level of adrenocortical activity. Most of the experimental studies in animals have been performed with large doses of thyroid substances over relatively short periods. The failure to find increased adrenal function in most patients with hyperthyroidism might be due to an accommodation to the hypermetabolic state. Some evidence suggesting such a process in guinea pigs is seen in the return of adrenal activity towards the normal level with continued dosage of thyroxine (Fig. 8).

Fourthly, an attractive argument can be made for a difference in pituitary function in Graves' disease and in hyperthyroidism induced in animals by thyroid administration. If one accepts for the purposes of discussion the theory that Graves' disease is caused by an increased secretion of thyrotropin, it might be suggested that under such circumstances the release of ACTH is inhibited. Thus an inverse relationship between the release of TSH and ACTH by the pituitary (an increase in TSH with a corresponding decrease in ACTH) would provide an explanation for the

normal or low steroid values which have been previously observed in Graves' disease. A condition resembling spontaneous hyperthyroidism in man has been described by Kracht (24) in wild rabbits brought into the laboratory under stressful conditions. In these animals tachycardia, tremor, weight loss, increased food intake and thyroid follicular hyperplasia developed. The adrenal cortices, however, were found to be small. The increased adrenal activity in hyperthyroidism induced by thyroid administration could also be explained by this hypothesis, in that a suppression of TSH by the exogenous thyroid would facilitate ACTH secretion. A direct effect of thyroxine on the pituitary may explain the guinea-pig experiments in which adrenal response correlated better with the dose of thyroxine than with the metabolic rate. For any given dosage of thyroxine, the resulting adrenal activity became highest several days prior to the maximal increase in the metabolic rate. The mechanism of production of the hyperthyroid state rather than the hypermetabolism per se may, therefore, be of major importance in regulating adrenocortical activity.

In primary myxedema, due either to absence of the thyroid or to antithyroid drugs, TSH may be increased and ACTH decreased with a resulting reduction in adrenocortical activity. This last concept has been previously suggested by Zarrow and Zarrow (25).

The therapeutic use of adrenocortical steroids in thyrotoxic crisis has been recommended by Rawson (26), who reported rapid improvement in 5 such patients treated with large doses of adrenocortical extract. Szilagy (27) obtained similar beneficial effects with ACTH; and Rukes (28) suggested the use of intravenous hydrocortisone in such situations. An opportunity has not been available to us to make a careful study of adrenal function in thyroid crisis, using modern methods. However, the finding of a normal or low excretion of adrenal steroids combined with evidence for increased utilization would suggest the possible development of a relative degree of adrenal insufficiency in these very toxic patients and would support the therapeutic use of these steroid agents.

SUMMARY

A study of the rate of disappearance of hydrocortisone from the plasma indicates a slow rate of steroid degradation in myxedema and an accelerated rate in hyperthyroidism as compared to control subjects. This rapid clearance of plasma 17-OH-CS in hyperthyroidism cannot be explained by an increased rate of urinary excretion.

The excretion of urinary 17-ketosteroids and 17-hydroxycorticosteroids (17-OH-CS) is within the normal range in hyperthyroidism, but is low in myxedema. The finding of a normal plasma level of 17-OH-CS in myxedema may be attributed to the decreased rate of steroid degradation.

The administration of thyroxine to the guinea pig increases adrenocortical activity as measured by urinary 17-OH-CS excretion. The excretion of 17-OH-CS appears to be related more directly to the dosage of administered thyroxine than to the metabolic rate.

An inverse relationship between TSH and ACTH secretion by the pituitary is suggested to explain the discrepancy between the increased adrenocortical activity in animals treated with thyroid and the normal or decreased activity in Graves' disease.

Because of the suggested decreased secretion of ACTH in Graves' disease and the increased rate of steroid utilization, the use of cortisone or hydrocortisone in the therapy of thyroid crisis is recommended. The failure to find increased adrenal function in clinical hyperthyroidism and the evidence suggesting an increased hydrocortisone requirement support the previously suggested therapeutic use of cortical steroids in thyroid crisis.

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REFERENCES

1. Hill, S. R., Jr.; Reiss, R. S.; Forsham, P. H., and Thorn, G. W.: The effect of adrenocorticotropin and cortisone on thyroid function: thyroid-adrenocortical interrelationships, *J. Clin. Enodcrinol.* **10**: 1375, 1950.
2. Wolfson, W. Q.; Beierwaltes, W. H.; Robinson, I. F.; Duff, J. R.; Jones, J. R.; Knorpp, C. T., and Eya, M.: Corticogenic hypothyroidism: its regular occurrence and clinical significance during prolonged therapeutic administration of ACTH or cortisone, *J. Lab. & Clin. Med.*, **36**: 1005, 1950.
3. Money, W. L.; Kraintz, L.; Fager, J.; Kirschner, L., and Rawson, R. W.: The effects of various steroids on the collection of radioactive iodine by the thyroid gland of the rat, *Endocrinology* **48**: 682, 1951.
4. Marine, D.: Remarks on the pathogenesis of Graves' disease, *Am. J. M. Sc.* **180**: 767, 1930.
5. LeCompte, P. M.: Width of adrenal cortex in lymphatic leukemia, lymphosarcoma, and hyperthyroidism, *J. Clin. Endocrinol.* **9**: 158, 1949.
6. Holst, J.: Pathologische Anatomie der Organe ausser der Schilddrüse bei der Basedow'schen Krankheit. Zweite internationale Kropfkonferenz, Bern (1933), Verhandlungsbericht, 1935, p. 62.
7. Means, J.: The Thyroid and Its Diseases, ed. 2. Philadelphia, J. B. Lippincott Co., 1948, p. 249.
8. Beierwaltes, W. H., and Bishop, R. C.: 17-Ketosteroid and pituitary follicle-stimulating hormone excretion in myxedema, before and during treatment with thyroxine, *J. Clin. Endocrinol. & Metab.* **14**: 928, 1954.

9. KENIGSBERG, S., and MCGAVACK, T. H.: The excretion of 17-ketosteroids. II. Values in several endocrine disturbances, *J. Clin. Endocrinol. & Metab.* **12**: 1551, 1952.
10. FRASER, R. W.; FORBES, A. P.; ALBRIGHT, F.; SULKOWITCH, H., and REIFENSTEIN, E. C., JR.: Colorimetric assay of 17-ketosteroids in urine. A survey of the use of this test in endocrine investigation, diagnosis, and therapy, *J. Clin. Endocrinol.* **1**: 234, 1941.
11. ENGSTROM, W. W., and MASON, H. L.: The excretion of 17-ketosteroids in patients with hyperthyroidism and myxedema, *J. Clin. Endocrinol.* **4**: 517, 1944.
12. DAUGHADAY, W. H.; JAFFE, H., and WILLIAMS, R. H.: Adrenal cortical hormone excretion in endocrine and nonendocrine disease as measured by chemical assay, *J. Clin. Endocrinol.* **8**: 244, 1948.
13. PERKOFF, G. T.; SANDBERG, A. A.; NELSON, D. H., and TYLER, F. H.: Clinical usefulness of determination of circulating 17-hydroxycorticosteroids levels, *A.M.A. Arch. Int. Med.* **93**: 1, 1954.
14. TALBOT, N. B.; SOBEL, E. H.; MCARTHUR, J. W., and CRAWFORD, J. O.: Functional Endocrinology from Birth through Adolescence. Cambridge, Mass., Harvard Univ. Press, 1952, p. 31.
15. HOSKINS, R. G.: Thyroid secretion as a factor in adrenal activity, *J.A.M.A.* **55**: 1742, 1910.
16. LOWENSTEIN, B. E., and ZWEMER, R. L.: A thyroid-adrenal relation in resistance to potassium, (abstract) *Endocrinology* **30**: S1035, 1942.
17. DEANE, H. W., and GREEP, R. O.: A cytochemical study of the adrenal cortex in hypo- and hyperthyroidism, *Endocrinology* **41**: 243, 1947.
18. LEBLOND, C. P., and HOFF, H. E.: Effects of sulfonamides and thiourea derivatives on heart rate and organ morphology, *Endocrinology* **35**: 229, 1944.
19. BAUMANN, E. J., and MARINE, D.: Involution of the adrenal cortex in rats fed with thiouracil, *Endocrinology* **36**: 400, 1945.
20. ZARROW, M. X., and MONEY, W. L.: Involution of the adrenal cortex of rats treated with thiouracil, *Endocrinology* **44**: 345, 1949.
21. SILBER, R. H., and PORTER, C. C.: The determination of 17,21-dihydroxy-20-ketosteroids in urine and plasma, *J. Biol. Chem.* **210**: 923, 1954.
22. NELSON, D. H., and SAMUELS, L. T.: A method for the determination of 17-hydroxycorticosteroids in blood: 17-hydroxycorticosterone in the peripheral circulation, *J. Clin. Endocrinol. & Metab.* **12**: 519, 1952.
23. BURSTEIN, S., and DORFMAN, R. I.: Hydrocortisone in normal guinea pig urine: isolation and quantitative determination, *J. Biol. Chem.* **206**: 607, 1954.
24. KRACHT, J.: Fright-thyrotoxicosis in the wild rabbit. A model of thyrotrophic alarm-reaction, *Acta endocrinol.* **15**: 355, 1954.
25. ZARROW, M. X., and ZARROW, I. G.: Mechanism of adrenal involution in the rat after treatment with thiouracil, *Proc. Soc. Exper. Biol. & Med.* **76**: 620, 1951.
26. RAWSON, R. W., and RALL, J. E.: Diseases of the thyroid, *in* Duncan's Diseases of Metabolism, ed. 3. Philadelphia, W. B. Saunders Co., 1952, p. 1007.
27. SZILAGY, D. E.; MCGRAW, A. B., and SMYTH, N. P. D.: The effects of adrenal cortical stimulation on thyroid function, *Ann. Surg.* **136**: 555, 1952.
28. RUKES, J. M.; ORR, R. H., and FORSHAM, P. H.: Clinical uses of intravenous hydrocortisone, *Metabolism* **3**: 481, 1954.

TREATMENT OF TOXIC ADENOMATOUS GOITER BY LARGE DOSES OF RADIOACTIVE IODINE*

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AT TIMES surgery is eliminated in the selection of a method of treatment for toxic adenomatous goiter, either because the patient refuses it or because his physical condition makes him a poor surgical risk.

The therapy usually next considered is the administration of an antithyroid drug, such as propylthiouracil. This method is highly useful in preoperative preparation or as definitive treatment in selected cases of Graves' disease, but unfortunately has several drawbacks in the treatment of multinodular goiter. Many months of therapy may be necessary before the hyperthyroidism is controlled, the remission effected may be only temporary, and in a few patients the drug has to be discontinued because of toxic effects. Therefore, the administration of radioactive iodine, although not considered the treatment of first choice in most cases, may become first choice under certain circumstances.

Previously, the dosage plan in the treatment of toxic adenomatous goiter has generally consisted of an initial dose of less than 20 millicuries, followed by small doses as necessary. In some instances, the total amount of radioactive iodine used has been as much as 100 millicuries (1). The disadvantage of this plan is the long period before hyperthyroidism is adequately controlled (2, 3)—usually from six to twelve months.

By the use of a dosage plan consisting of a large initial dose of radioactive iodine, the hyperthyroidism of toxic adenomatous goiter appears to be controlled more promptly and effectively than when the initial dose is

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small. Frequently, the disease is controlled within two to four months. This is comparable to the length of time usually required to control the hyperthyroidism of Graves' disease when I^{131} is administered, or to the length of time required for preoperative preparation and recovery after surgery in many patients with multinodular goiter.

CLINICAL MATERIAL AND METHOD

Between 1952 and 1954, 31 patients having toxic adenomatous goiters, who had either refused surgery or were considered poor surgical risks,

TABLE 1. RESULTS OF TREATMENT OF TOXIC ADENOMATOUS GOITER WITH I^{131} (initial dose, 20–40 mc.)

Case No.	Initial dose of I^{131} (mc.)	First time disease known to be controlled	Additional dose (mc.)	Estimated size of thyroid (Gm.)	Thyroidal I^{131} uptake (%)		B.M.R. (%)	
					Before therapy	After therapy	Before therapy	After therapy
1	20	4 mo.	30	50	24	30	+29	+ 2
2	25	2 mo.			50	31	+28	− 3
3	30	4 mo.	30	substernal	40	5	+29	+ 1
4	30	2 mo.		50	31	11	+48	− 5
5	20	4 mo.	30	75	37	9	+45	+ 7
6	30	4 mo.		75	55	11	+59	+10
7	20	4 mo.	20	70	33		+36	+ 5
8	30	2 mo.		85	39	20	+24	+ 1
9	25	3 mo.		100	54		+15	−14
10	25	4 mo.	25	120	19	13	+48	+12
11	30	2 mo.		65	66	19	+83	+19
12	40	2 mo.		50	50	10	+26	+25
13	30	(toxic after 4 mo.)	30	100	29	31	+59	+26
14	30	6 mo.	30	70+ (substernal)	59	17	+60	+17
15	20	12 mo.	20–25	70	69	15	+40	+ 5
16	30	16 mo.	20–20	80	68	10	+50	−11
17	30	9 mo. (low uptake at 4 mo.; no further I^{131} given)	30	50	47	10	+33	+ 4
18	40	(toxic after 6½ mo.)		substernal	47	0	+42	+34
19	40	4 mo.		60–70	58	9	+39	+ 1
20	25	2 mo.		60	58		+37	+14
21	20	3 mo.		50	67	24	*	+ 1

* B.M.R. not determined because patient was uncooperative. Two serum protein-bound iodine values were elevated above normal prior to I^{131} therapy.

were treated with large initial doses of radioactive iodine. Twenty-one received an initial dose of 20 to 40 millicuries (Table 1, Cases 1–21) and 10 received an initial dose of 50 millicuries or more (Table 2, Cases 22–31).

It has been our belief that the irregular distribution of I^{131} in multinodular goiter as well as the large size of the gland may be factors influencing the speed and the completeness of control after I^{131} therapy.

TABLE 2. RESULTS OF TREATMENT OF TOXIC ADENOMATOUS GOITER WITH I^{131} (initial dose, 50 mc. or more)

Case No.	Initial dose of I^{131} (mc.)	First time disease known to be controlled	Additional dose (mc.)	Estimated size of thyroid (Gm.)	Thyroidal I^{131} uptake (%)		B.M.R. (%)	
					Before therapy	After therapy	Before therapy	After therapy
22	50	4 mo. Euthyroid		80	45		+22	0
23	50	4 mo.	50	substernal	39	32	+53	− 1
24	50	3 mo.		50	65	10	+35	+10
25	50	2 mo.		75	68	14	+21	− 6
26	50	4 mo.	50	substernal	39	7	+53	− 1
27	50	4 mo.		60	54	28	+39	+21
28	50	3 mo.		100	31	29	+24	+ 4
29	50	Toxic after 5 mo. (uptake dropped to 4%); 18 mo. euthyroid		180	34	4	+40	+10
30	70	Toxic in 4 mo. (uptake dropped to 4%); improved at 6 mo.		125	25	5	+47	+23
31	50	4 mo.	25	substernal	47	0	+46	−13

Despite this, there has been a growing impression that those patients who received the larger doses got well faster. Most of our patients receiving doses of 50 mc. or above, had goiters estimated as weighing 75 grams or more.

Although the differential diagnosis between a toxic adenomatous goiter and Graves' disease in a pre-existing adenomatous goiter is sometimes difficult, we believe that no examples of Graves' disease have been included in the cases reported here. The differential diagnosis was on a clinical basis. Each patient had one or more basal metabolism determinations (Table 1), one or more I^{131} tracer studies, and was seen by at least two consultants on the metabolic service. Patients having a solitary adenoma, those having small nodular glands estimated to weigh less than 50 grams, and those in whom the diagnosis was in doubt, were not included in the group.

At the high dosage levels of I^{131} employed here, it would be expected that a patient having Graves' disease would become myxedematous. Patients having toxic adenomatous goiters, however, rarely become myxedematous following treatment with I^{131}, no matter what dose is employed. The fact that myxedema has not occurred in any of these patients seems to corroborate the correctness of the diagnoses.

Other than the existence of a multinodular goiter, there was no clinical evidence to arouse suspicion of malignancy in any of these patients. In our experience and those of others, malignancy is a rare occurrence (4, 6, 7). Crile and Dempsey (6) have estimated that the incidence of thyroid

cancer in patients such as these (no clinical suspicion of malignancy) is about 1 in 6,000.

The risk of inducing malignant change at some future time was not considered to be significant. During its many years of use, radioactive iodine has never been reported as the cause of cancer.

Twenty-nine of the 31 patients in this group were more than 50 years of age; 22 were more than 60; 7 were between 50 and 60; and 2 were between 45 and 50 years old. The estimated sizes of the goiters in the series ranged between 50 and 200 grams.

RESULTS

The part of the problem which interested us most was the length of time required for complete control of the hyperthyroidism. Fifteen of the 21 patients who received 20 to 40 millicuries as an initial dose were euthyroid within four months. Of these 15, 6 became euthyroid in two months, 2 within three months, and 7 within four months. Five patients of this group required the administration of an additional 20 to 25 millicuries two months after the first dose.

In 4 patients who received between 20 and 40 mc. as an initial dose, control was not obtained within four months. They eventually became euthyroid at six, nine, twelve and sixteen months, respectively, after additional doses. In these patients the total amounts of iodine used ranged between 60 and 70 millicuries.

One patient who received an initial dose of 20 to 40 mc. and was toxic after four months, was not given more I^{131} because of a persistent thyroid uptake of less than 10 per cent. The remaining patient was toxic at six and a half months and has not been seen since.

Eight of the 10 patients who received 50 millicuries or more as the initial dose were euthyroid within four months. Of these, 1 was euthyroid in two months, 2 within three months, and 5 within four months. In this group of 8 patients, 3 were given additional doses of I^{131}, 2 receiving 50 mc. and 1 receiving 25 mc. All additional doses were given two months following the initial dose. One of the 2 patients who were not euthyroid within four months became euthyroid at the end of eighteen months, and the other was toxic at six months but no further data could be obtained.

To substantiate our claim that large doses of I^{131} are more effective than small doses in controlling the hyperthyroidism of toxic adenomatous goiter, we have compared our findings with those in two other series (3, 5) previously reported (1950, 1951) from the Cleveland Clinic (Table 3). A comparison of the percentage of patients in each of the three series who had a remission of hyperthyroidism after only one dose of I^{131} is significant. Of the 37 patients reported in 1950, the initial dose ranged from 7 to 28

TABLE 3. COMPARISON OF THREE SERIES

Series	No. of patients	Initial dose of I^{131} (mc.)	Remission after one dose (% of patients)	Range of total dose (mc.)	Avge. dose (mc.)	Avge. No. of doses	Mean time (months) to obtain remission	Remission in 4 mo. (% of patients)
Richards, Crile & McCullagh, 1950, (5)	37	7–28, generally less than 20	8.1	7–104	37.3	3+	not available	16.2
McCullagh & Richards, 1951, (3)	78	generally less than 20	8.6 (BMR> +40) 14 (BMR < +40)	7–104	34	2 mean 2.4	6.4 (BMR > +40) 7.0 (BMR < +40)	not available
Cook, Jones & McCullagh	21	20–40	47.6	20–70	43.2	1+ mean 1.5	4.89	71.4
	10	50	70	50–100	60.4	1+ mean 1.3	5	80

mc. and usually was less than 20 mc. In 8 per cent of the patients the disease was controlled with one dose. The 1951 report concerned 78 patients. The doses used were similar to those used in 1950, and in approximately 10 per cent of this group the disease was controlled by a single treatment. In the present series the thyrotoxicosis was controlled in 48 per cent of 21 patients receiving a single dose of 20 to 40 mc., and in 70 per cent of 10 patients receiving a single dose of 50 mc. or more.

There was no instance of increased thyrotoxicosis or of aggravation of the patient's cardiac status following large amounts of radioactive iodine. Radiation thyroiditis developed in 2 of these patients, but in each case it was very mild and did not require treatment.

In our experience, the initial thyroidal radioactive iodine uptake and the basal metabolic rate seem to bear little relationship to the length of time between the initial therapeutic dose and control of the hyperthyroidism. A normal iodine uptake in the presence of a multinodular goiter does not exclude the presence of thyrotoxicosis. The uptake tracer measurements were above 50 per cent in only 12 of the 31 patients.

Substernal extension of the thyroid was not considered a contraindication to radioiodine therapy and in a few such cases the size of the gland was reduced remarkably. The usual reduction was approximately 50 per cent.

The use of radioactive iodine in the treatment of a toxic adenomatous goiter has limitations. Control of the hyperthyroidism was not achieved within a four-month period in 8 patients. One reason for failure was that further treatment could not be attempted because of radioiodine uptakes of 10 per cent or less in the presence of continued thyrotoxicosis: stable

iodine could not have been a factor, as the low iodine uptakes occurred in 5 patients, none of whom had been given stable iodine prior to radioactive iodine therapy and all of whom had an initial uptake in the range of 25 to 68 per cent. Four of these patients subsequently became euthyroid without further treatment. The fifth patient had received an initial dose of 30 mc. and was still toxic after four months, following which time further follow-up was not possible.

We do not yet regard therapy with large doses of radioactive iodine as the treatment of choice for a toxic multinodular goiter when expert thyroid surgery is available, acceptable to the patient, and the calculated risk is less than 0.5 per cent. If results in "high-risk patients" remain good or are improved, it may be that in the future large doses of I^{131} will be considered desirable in a much larger proportion of patients having this type of goiter.

SUMMARY

Thirty-one patients with toxic adenomatous goiter were treated with a large initial dose of radioactive iodine; in 23 the hyperthyroidism was controlled within four months. Following an initial dose of 50 mc. or more, the hyperthyroidism appeared to be controlled more promptly and effectively than following a smaller initial, or a smaller repeated dose.

In no instance was the cardiac status aggravated by treatment. In some patients the initial therapy did not control the hyperthyroidism, but further treatment with radioactive iodine resulted in a euthyroid condition. In others the thyroidal uptake of radioactive iodine was too low, despite persistent thyrotoxicosis, to warrant repeated administration.

When treatment other than surgery is to be used in toxic multinodular goiter, radioactive iodine should be given first consideration.

REFERENCES

1. Clark, D. E.; Trippel, O. H., and Sheline, G. E.: Diagnostic and therapeutic use of radioactive iodine, *A.M.A. Arch. Int. Med.* **87**: 17–24 (Jan.) 1951.
2. Thompson, W. O.: The present status of the treatment of toxic goiter, *J. Clin. Endocrinol. & Metab.* **12**: 130–134 (Jan.) 1952.
3. McCullagh, E. P., and Richards, C. E.: Radioactive iodine in treatment of hyperthyroidism, *A.M.A. Arch. Int. Med.* **87**: 4–16 (Jan.) 1951.
4. Lahey, F. H. (moderator): Panel discussion: Adenomatous goiter, *Tr. Am. Goiter A.* pp. 219–234, 1953.
5. Richards, C. E.; Crile, G., Jr., and McCullagh, E. P.: Radioactive iodine in the treatment of the hyperthyroidism of nodular goiter, *J. Clin. Endocrinol.* **10**: 1077–1083 (Sept.) 1950.
6. Crile, George, Jr., and Dempsey, W. S.: Indications for removal of nontoxic nodular goiters, *J.A.M.A.* **139**: 1247–1250 (Apr. 30) 1949.
7. Zimmerman, L. M., and Wagner, D. H.: Carcinoma of the thyroid gland: its incidence and relation to nodular goiter, *Tr. Am. Goiter A.* pp. 287–294, 1953.

Teaching Clinic

PRECOCIOUS PUBERTY OF THE FEMALE TYPE

THE appearance of the menarche before the age of 9 should be considered precocious, warranting investigation of the cause of the vaginal bleeding. The great majority of girls who have an early menarche are simply manifesting early sexual maturation without organic disease, *i.e.*, "constitutional precocity." In such a child there is early appearance of the hormonal pattern characteristic of the more mature girl; the ovaries respond to stimulation by pituitary gonadotropin, secreting estrogen, which causes the development of secondary sexual characteristics. These are normal children whose sexual maturation occurs earlier than is usually expected and in whom the prognosis is for continued normal physical development but early epiphyseal closure. A similar hormonal pattern appears in girls whose pituitary activity is stimulated by a lesion in the hypothalamus. In these patients, however, the prognosis is dependent upon the progress of the hypothalamic lesion.

In contrast are patients who manifest sexual precocity because of estrogen formed by an autonomous steroid-secreting structure, such as a granulosa-cell tumor of the ovary or a feminizing adrenal tumor. In these cases the gonads are not stimulated by gonadotropin, but independently secrete gonadal steroids to such an extent that the pituitary is probably suppressed. Another different, but rare type of hormonal pattern is found in patients with precocity due to a neoplasm which itself produces gonadotropin. This condition is exemplified by the patient with a teratoma which secretes chorionic gonadotropin and thereby stimulates ovarian secretion. The following cases illustrate these types of precocity.

CASE I

Chief complaint: The patient was a 7½-year-old girl who first had vaginal bleeding one week before admission.

Present illness: One week before admission the patient had painless vaginal bleeding requiring several pads daily and lasting for four days. The patient's general health had been excellent. Her birth weight was 7½ pounds. Her early developmental pattern was normal. She had always been an active, well-coordinated, intelligent, fairly large child. During the preceding two and a half years she had been at least 2 inches taller than her contemporaries and was the tallest girl in her class in school. She did well in school and was considered by the teachers to be one of the leaders of the children. For the preceding six months the parents had been aware of slight breast development. For the preceding

two months a slight amount of pubic hair (but no axillary hair) had been noted. There were no other indications of endocrine disturbance.

Past history: The patient had never been seriously ill.

Family history: The father's height was 6 feet 2 inches. He weighed 190 pounds. Sexual development was said to have occurred at an early age. The mother's height was 5 feet 9 inches, and her weight 145 pounds. Her menarche had occurred at the age of 12. Two brothers and one younger sister were healthy and fairly large for their ages.

Physical examination: The patient was a symmetrically developed, large, alert, intelligent and cooperative girl who was 4 inches taller than average for her age. Her skin was soft, smooth, and of normal moisture and texture. Hair of the head was normal in amount and texture. The hips were moderately well padded. The breasts were in the areolomamma stage. There was a slight amount of pubic hair but no axillary hair. The external genitalia were moderately mature in appearance, with well developed labia minora. On rectal examination the uterus was about one quarter the adult size. The uterocervical ratio was approximately 1:1. No adnexal masses were felt. The rest of the findings on physical examination were not remarkable.

Laboratory data: Results of a complete blood count and urinalysis were within normal limits. The vaginal smear contained a moderate number of cornified cells. Roentgenograms of the sella turcica were reported as being normal and films of the epiphyses were interpreted as showing a bone age of 9½ years. Gonadotropin excretion was 8 mouse uterine units per twenty-four hours, and 17-ketosteroid excretion was 2.36 mg. per twenty-four hours.

Diagnosis: Constitutional sexual precocity.

Course: For the next six months the patient's menstrual cycle was irregular. Subsequently it became regular, with a 28-day interval. Her growth continued at a rapid rate for the next four years and then ceased. At present, seven years after being studied, the patient is doing well in school and is psychologically well adjusted.

In this patient, diagnosis was based principally on the absence of detectable organic lesions and the presence of an orderly pattern of sexual maturation. Gonadotropin and estrogen secretion were moderately increased in an amount compatible with the degree of sexual maturation. In such instances, premature bone maturation results from the early production of estrogen. It induces sufficiently early closure of the epiphyses to cause the patient to become a somewhat short adult.

In handling these cases one encounters essentially psychologic problems. In Case I, the patient had an excellent result because of intelligent management by her parents. A poor outcome is usually due to rejection or lack of insight on the part of the parents. It is particularly important that they assume a positive approach with these children. The parents should he helped to educate the child as much as possible about the physiologic events which are taking place and to assume an attitude of acceptance without shame or excessive secretiveness.

It is also important that parents and teachers attempt to reconcile in their own minds the physical maturation with the emotional and intellectual immaturity. Failure to recognize this disparity may lead to aggra-

vation of already serious emotional problems by unsympathetic punishment for acts which are not motivated by malice but rather are the result of the child's relatively great strength in comparison with children of the same age.

CASE II

Chief complaint: The patient was an 8½-year-old girl who had had cyclic vaginal bleeding for one year.

Present illness: Birth was normal, and the birth weight was 7 pounds. Juvenile development was delayed. The patient first walked at 18 months and did not begin to talk until the age of 2½ years. She was always a large child. At the age of 5 she was first noted to have slight enlargement of the breasts. This enlargement had continued to the time of examination. For about the previous eighteen months she had had pubic hair, and recently had grown considerable axillary hair. Spontaneous vaginal bleeding first occurred one year before examination. The cycle varied from twenty-five to forty days, with periods of bleeding as long as ten days. The patient was mentally deficient. She attended a special school and had achieved development equivalent to that of a first-grade child. No stigmata of other endocrine disease were described.

Past history: No serious illnesses.

Family history: Not contributory.

Review of systems: Not contributory.

Physical examination: The patient was a large, symmetrically developed, mentally dull child who was 5 inches taller than the average for her age; she was well femininized, with large breasts, definite padding of the hips, considerable pubic hair and a moderate amount of axillary hair. The patient was menstruating. Visual fields were normal. On rectal examination the uterus was found to be small adult size with a uterocervical ratio of 2:1; no adnexal masses were felt. Otherwise, the results of physical examination were not remarkable.

The x-ray report stated that nothing abnormal was noted in the sella turcica. Roentgenograms of the epiphyses were interpreted as showing a bone age of 14 years. A pneumo-encephalogram demonstrated enlargement and displacement of the third ventricle. The urinary gonadotropin titer was positive at 16 mouse uterine units per twenty-four hours. The vaginal smear contained many well cornified epithelial cells.

Impression: Sexual precocity probably due to stimulation of the pituitary by a hypothalamic lesion.

Course: A regular 28-day menstrual cycle developed in this patient. The presence of premenstrual molimina suggested that she ovulated. She continued to attend a special school for retarded children.

Prognosis in such patients depends upon the course of the hypothalamic lesion; in this case it did not appear to be neoplastic and was probably not progressive. This patient had an endocrine pattern essentially similar to that present in Case I. There was ovarian function of a degree comparable to that found in an older girl, with corresponding sexual development. The release of gonadotropin which stimulated the ovaries was undoubtedly an unusual hypothalamic effect (presumably neurohumoral) resulting from a hypothalamic defect. Lesions of this type can cause either stimulation or

inhibition of the release of gonadotropin; the difference in response probably depends on the exact location and size of the lesion. Some lesions presumably destroy nuclei which are concerned with stimulating the pituitary, and thereby cause a decrease in the release of gonadotropin. Other lesions possibly either destroy nuclei which regulate the secretion of substances having a chalonal or depressing effect on the pituitary, or else increase the function of nuclei which stimulate the release of pituitary gonadotropin. In either case, precocious release of gonadotropin would occur.

The next case illustrates precocity resulting from secretion of estrogen by an ovarian neoplasm.

CASE III

Chief complaint: The patient was a 4-year-old child who had had vaginal bleeding, enlargement of the breasts and pubic hair growth.

Present illness: The patient was a normal baby with a birth weight of 7 pounds. Development was normal. Eleven months before admission there had been a vaginal discharge. Seven months before admission the patient had had an episode of vaginal bleeding which lasted two days. About one month before admission she was first noted to have enlarging breasts. For several months she had had a small amount of pubic hair.

Past history: At the age of 1½ years several rectal polyps had been removed.

Family history: Not contributory.

Physical examination: The patient was a well developed, large (3 inches taller than average) symmetrical, well nourished child who was intelligent and cooperative. The skin was smooth, soft and without acne. The hair of the head was normal in texture and oiliness. A slight growth of pubic hair was present but no axillary hair. Breasts were in the bud stage with large, dark nipples. The external genitalia were relatively mature; the clitoris was not enlarged; the labia minora were moderately well developed. By rectal examination under anesthesia the uterus was found to be about 4 centimeters in length. Neither adnexal masses nor ovarian enlargement were noted.

Laboratory data: The vaginal smear contained many cornified cells. X-ray examination showed the sella turcica to be normal and roentgenograms of the epiphyses were interpreted as representing a bone age of 8 years. Urinary 17-ketosteroid excretion was 2.0 mg. per twenty-four hours. The urinary gonadotropin titer was less than 4 mouse uterine units per twenty-four hours in six specimens and positive at 2 mouse units in one specimen. Urinary estrogen excretion was determined by bioassay and was found to be equivalent to 22 micrograms of estrone per twenty-four hours. Pregnanediol excretion was 3.3 mg. per twenty-four hours.

Course: Following the initial studies, the patient was neither seen nor heard from for one year. When she returned it was reported that during this time she had repeated episodes of uterine bleeding in cycles approximating twenty-eight days. One month before she returned, bleeding had become almost continuous, with at least spotting every day. However, it had not been sufficient to produce anemia. Urinary gonadotropin determination yielded negative results at a level of 4 mouse uterine units per twenty-four hours, and 17-ketosteroid excretion was 2 mg. per twenty-four hours. The vaginal smear contained many cornified cells. An intravenous pyelogram did not demonstrate any abnormal findings. Roentgenograms of the epiphyses were interpreted as showing a bone age of 11 years. At laparotomy the right ovary was found to be about twice the size of the left. It

was removed entirely, and a diagnosis of "luteoma" was made on the basis of histologic examination. Two weeks after operation urinary gonadotropin determination yielded positive results at a level of 8 mouse uterine units per twenty-four hours. Three months after operation a striking decrease in the degree of cornification of the vaginal epithelium and a definite decrease in size of the breasts had occurred.

In this patient, the first signs of precocity developed at an earlier age than in the other 2 patients, and the clinical as well as laboratory evidence indicated higher levels of estrogen excretion than in the other subjects. The failure to find significant amounts of gonadotropin in eight attempts suggested that the high level of estrogen was not the result of ovarian stimulation by the pituitary. The dramatic increase in the bone age within a period of one year was also indicative of relatively large estrogen effects. The absence of a palpable tumor at the initial examination was not surprising, because at operation some time later the tumor was no greater than twice normal ovarian size.

Any child who has rapid onset of precocity with evidence of high urinary estrogen levels without high gonadotropin levels should be presumed to have a neoplasm and should be surgically explored. The most probable site of the neoplasm is the ovary, although feminizing tumor of the adrenal should be kept in mind.

The fourth case concerns a patient who had a tumor producing gonadotropin which stimulated the ovary.

CASE IV

Chief complaint: The patient was a 5-year-old girl, admitted because of enlargement of the breasts, vaginal bleeding and an abdominal mass.

Present illness: About eight months before admission the patient had complained of ill-defined abdominal pain. About four months before admission she was first noted to have breast enlargement. The patient had grown rapidly in the six months before entry; one month before, she had had slight vaginal bleeding. One week before admission she consulted a physician, who found the genitalia to be unusually mature and palpated an abdominal mass which extended above the pubis.

Physical examination: The patient was a large, well developed, well nourished child who was 3 inches taller than the average for her age, and who was alert, intelligent and cooperative. The skin was smooth, soft and of normal texture. There was a small amount of pubic hair, but no axillary hair. The breasts were in the primary bud stage. In the abdomen there was a palpable mass approximately the size of a grapefruit extending above the pubis. This mass was also felt on rectal examination and filled a major portion of the pelvis. The external genitalia were quite mature.

Laboratory data: On x-ray examination the sella turcica was reported to be normal, and films of the epiphyses were interpreted as indicating a bone age of 7 years. The vaginal smear showed a moderate number of cornified cells. Excretion of chorionic gonadotropin was estimated as 2,000 international units per twenty-four hours. Urinary 17-ketosteroid excretion was 2 mg. per twenty-four hours.

Course: At laparotomy the patient was found to have a large round tumor arising

from the right ovary. This was removed and a diagnosis of teratoma was made on the basis of examination of a frozen section. The contralateral ovary was at least twice the size expected in a child of 5. The uterus was also considerably enlarged, having a utero-cervical ratio of about 1:1. Because of the high incidence of malignancy in such tumors and the high frequency of simultaneous occurrence in, or of metastasis to, the contralateral ovary the consulting pathologist and the surgeon decided on the performance of a panhysterectomy and bilateral oophorectomy. The postoperative course was uneventful. One week following operation no gonadotropin was detectable in the urine.

In this case the ovarian neoplasm produced gonadotropin which stimulated the contralateral ovary, and this in turn caused growth of the uterus and vaginal bleeding. No evidence has yet been reported that such neoplasms produce steroid. In this particular instance it seems probable that all of the estrogen was formed by the opposite ovary. The surgeon's decision to remove the contralateral ovary because of the possibility of metastasis may be debated. Life expectancy in such patients is very poor. The incidence of malignancy in these tumors has been reported to be as high as 65 per cent, and widespread dissection of the pelvic contents has been recommended as a life-saving procedure. However, it must be recognized that such tumors are not always bilateral and that conservation of the opposite ovary and a close follow-up might very well be successful. The bilateral oophorectomy introduced a serious problem: If the patient survives to puberty, she will require careful estrogen substitution therapy in order to grow normally. If the estrogen is not given in adequate amounts, the patients can be expected to manifest a hypogonadal body habitus with unusual tallness. On the other hand excessive estrogen therapy may result in premature closure of the epiphyses and shortness. In contrast to the other patients presented, whose problems required the services of an endocrinologist only for recognition and immediate solution, this patient will need continued endocrinologic supervision for most of her life.

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Editorial

ADRENOCORTICAL STEROIDS IN THE PERIPHERAL BLOOD OF MAN*

THE quantitative estimation of the adrenal corticosteroids in the peripheral blood of man is of much theoretical and practical interest. The amount of detectable adrenal steroids in circulating blood as determined by newly developed techniques has permitted the study of adrenocortical function in man. As a result, it has been possible to come to a better understanding of certain diseases related to adrenocortical dysfunction. The technical difficulties of the methods are such that they are not generally available as routine clinical procedures.

Although biologic and chemical methods (1, 2) for the estimation of adrenal corticosteroids in blood had been described earlier, Nelson and Samuels (3) are responsible for first devising more acceptable techniques through their continued discriminating studies. The determination of adrenal steroids in blood requires care and consideration for the specificity of the methods, in line with principles previously set forth in these pages (4).

It is hazardous to apply any of the colorimetric tests to crude extracts of plasma without some means of preliminary purification. Nelson and Samuels (3) employed a relatively simple chromatographic procedure; Sweat (5) has also described a similar preparatory step. By such means, many nonspecific substances are removed from the extracts. Although this precaution is time-consuming, its advantages are not to be overlooked. On the other hand, various workers have substituted plasma blanks of relatively crude extracts. This method requires larger volumes of blood—a matter of no little account, since the quantities ordinarily necessary are not small. Furthermore, in such blanks some of the reagents may produce color values that are so high as to approach the "test" values. Silber and Porter (6) have recommended a simpler method, wherein the colorimetric reagent itself is used to extract the corticosteroids from a much

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larger volume of the washed organic solvent, containing the plasma extract. This represents a great simplification in methodology and has already proved useful in some hands (7). In our hands the recovery of pure steroids with the latter method, after a brief trial, has been erratic; this may be related to the partition of such steroids between the large volume of organic solvent and the much smaller volume of the "Porter-Silber" reagent, a detail not well defined in any of the communications to date.

The particular reagent employed for the colorimetric measurement of the extracted corticosteroids is worthy of comment. The quantities of these steroids in blood are so small that the technique should be sensitive; it must also be reasonably specific and capable of detecting a wide group of steroid molecules representative of the adrenocortical secretions. Herein lies the dilemma—the desirability for maximum sensitivity and specificity without exclusion of the method from the realm of general utility. The "Porter-Silber" reagent (8) (phenylhydrazine in approximately 62 per cent sulfuric acid) is extremely sensitive and most widely used. It measures those compounds with a 17,21-dihydroxy-20-ketone function. In this laboratory compounds E (11-dehydro-17-hydroxycorticosterone), F (17-hydroxycorticosterone), S (17-hydroxy-11-desoxycorticosterone), and their reduced tetrahydro derivatives, all of which contain this chemical group, react equally well (within 15 per cent). Since the adrenal cortex of man is known to produce compound F predominantly, and since this steroid occurs in greatest quantity in the peripheral blood of man (9), the "Porter-Silber" reagent may be regarded as satisfactory. It does, however, react to produce similar colors with other compounds such as quinine and paraldehyde (10). The high concentration of sulfuric acid in the reagent produces colors with other organic compounds in extracts of plasma; this is minimized by suitable preparatory purification as discussed. The latter disadvantage may be overcome in part by the employment of a correction factor (3) based on the peak absorption of pure 17-hydroxycorticosteroids so treated at approximately 410 mμ. It has been suggested that hydrochloric acid (which causes less charring) be substituted for the sulfuric acid (11), but we have found that the sensitivity is then so reduced that the minute quantities of steroids in 10 ml. of plasma are not detected. It is mandatory that the majority of plasma extracts measured with the "Porter-Silber" reagent in a given laboratory, exhibit maximal absorption at 410 mμ. It would not seem justified to persist in the employment of this technique when the latter requirement does not obtain for most specimens studied, with the exception of those containing very small quantities of corticosteroids, as in Addison's disease. Certain steroids possessing an 11-beta-hydroxyl group, such as compounds F and B (corticosterone) exhibit marked fluorescence in absolute ethanol and

concentrated sulfuric acid (12); the fluorometric method is perhaps the most sensitive, but is not highly specific; hence great care must be exercised in the preparatory purification of extracts. It has the advantage of detecting compound B, which will not react with the "Porter-Silber" reagent. However, the quantities of compound B ordinarily found in human blood are probably insignificant as compared to compound F (9). It is possible to use 2,4-dinitrophenylhydrazine (13), which reacts with available carbonyl groups, and may also yield higher values than does the "Porter-Silber" reagent. Blue tetrazolium, a reagent which measures the reducing alpha ketolic steroids without relationship to the 17-hydroxy group has also been employed, following the preliminary purification of extracts of plasma on paper (14); the results reported are higher than those with the "Porter-Silber" reagent, since a larger spectrum of steroids may be so detected. The last two methods are highly sensitive under appropriate conditions. The values obtained will vary considerably due to differences in the reactive groups measured by each reagent. It is not possible to state which is the most accurate. There is a tendency to favor a given method because it yields the greatest values, *i.e.*, "the highest man wins." Further work is necessary to correlate the various methods with more precise qualitative and quantitative tools in order to determine the "best," although admittedly several may serve the purpose.

Fukushima *et al.* (15) have demonstrated the presence of steroids in human urine which are reduced at C-20 and may account for 30 per cent of the metabolites of compound F. There is already evidence that such compounds may occur in human blood (16), but the majority of reagents discussed here will not detect their presence. The method of chromic-acid oxidation employed by Wilson (17) should detect such steroids and, in fact, much greater quantities of adrenocortical steroids are found in human blood by such means (18).

To date, most studies have considered only the free (unconjugated) corticosteroids present in human blood. In this laboratory significant amounts of steroids have been released by the hydrolysis of human plasma with beta-glucuronidase (19, 20). Hydrolysis with acid is not suitable. Definitive identification of such compounds, using the method of the authors has been obtained (16). The conjugated corticosteroids in blood usually appear to be the reduced tetrahydro derivatives of their active precursors and, although probably inactive, faithfully mirror adrenocortical function. Under some clinical circumstances the conjugated compounds may yield more reliable information than the free levels alone (20, 21). In one experiment, the repetitive oral administration of a steroid to a human volunteer resulted in the progressive rise of the conjugated corticosteroids to a level exceeding 3,000 micrograms per 100 ml. of plas-

ma, whereas the free level rose more slowly and did not exceed 300 micrograms (16). Under these artificial circumstances the conjugated level was a more reliable index of the quantity of administered steroid than the free level.

The continued interest in the plasma corticosteroids of man is based in part on the desirability of evaluating adrenocortical function at a level nearer to the source of the hormones, without the interposition of renal factors. The corticosteroids occur in urine almost entirely in a reduced state, conjugated as glucuronosides. These conjugates have been isolated from urine (22). On the other hand, in blood, about 50 per cent of the total quantity we have measured is free and retains the structure of the active substances secreted by the adrenal gland. Under conditions of chronic hypersecretion of the adrenal cortex, the conjugated moiety occasionally may exceed the free (20). The difference between the urinary and plasma corticosteroids is in part attributable to renal clearance of the free versus the conjugated material. We have found that the free corticosteroids are cleared from plasma at a rate of 11.2 per cent and the conjugated, 71.0 per cent, as compared to the endogenous creatinine clearance (16) after the oral administration of large doses of a steroid. Such factors as the renal excretion and the conjugation are critical in the interpretation of the blood levels. In chronic hepatic disease, there is impaired conjugation of blood steroids following the oral administration of compounds E or F (20). As pointed out by Eik-Nes *et al.* (23), the blood level has meaning "only when there is a balance between endogenous production and removal" of corticosteroids. With respect to the "free" level alone, removal is attributable to conjugation more than to renal excretion.

The determination of plasma corticosteroids in man has been applied widely to the study of many clinical conditions which cannot be adequately reviewed. Among these, light has been shed on the disordered adrenocortical function in the adrenogenital syndrome and in rheumatic fever (24, 25). The greatest clinical value lies in the diagnosis of Addison's disease, and of Cushing's syndrome due to adrenocortical hyperplasia, or adrenocortical tumor. The base-line levels in each of these conditions is usually sufficiently distinctive to be of value. The response of the blood corticoid level to the administration of adrenocorticotropin may bring into better perspective a patient's adrenocortical status. The conditions under which these tests are conducted should be well controlled (26). Patients with Addison's disease respond poorly to ACTH, with little or no elevation in the concentration of blood corticosteroids, even though the base-line levels, at times, may be within the lower range of normal (7, 21, 27). In Cushing's syndrome, there is characteristically a hyper-responsivness to

ACTH, with the attainment of levels much greater than those in normal individuals following stimulation; this response diminishes after adequate subtotal adrenalectomy (21). The blood and urinary levels are also generally high in Cushing's syndrome due to adrenocortical tumor. With adrenal carcinoma there is little further increase with ACTH, whereas in some instances of adenoma a marked rise has been reported (7, 23, 28, 29). It is probable that the steroids measured in patients with adrenal carcinoma are different from those present in hyperplasia. Tetrahydro-S (pregnane-3(α),17(α),21-triol-20-one) has been found as a major component in the urine of patients with carcinoma (30, 31), whereas in hyperplasia the usual reduction products of compound F are found. Both types of steroids would react with the "Porter-Silber" reagent, which was employed in the studies cited. When the differential diagnosis must be made between hyperplasia and tumor, it may be helpful to distinguish the major component in blood or urine by paper chromatographic techniques. We have been able to distinguish compounds F and S extracted from human blood in this manner, when their levels were high.

It is hoped that further improvements in the methods for determining the adrenal corticosteroids in plasma are forthcoming. Until one or more of the procedures in use may be safely assumed to measure susbtances representative of the adrenocortical secretions and their metabolites in blood, the absolute results must be accepted with reservation. Due regard must be accorded the 20-hydroxylated and the conjugated corticosteroids, although it may ultimately be shown that these substances generally vary directly with those ordinarily estimated. Simplifications in techniques designed to facilitate clinical application of these tests are to be sought, so long as they do not significantly sacrifice specificity.

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REFERENCES

1. VOGT, M.: The output of cortical hormone by the mammalian suprarenal, *J. Physiol.* **102**: 341–356, 1943.
2. CORCORAN, A. C., and PAGE, I. H.: Method for the chemical determination of corticosteroids in urine and plasma, *J. Lab. & Clin. Med.* **33**: 1326–1333, 1948.
3. NELSON, D. H., and SAMUELS, L. T.: A method for the determination of 17-hydroxycorticosteroids in blood: 17-hydroxycorticosterone in the peripheral circulation, *J. Clin. Endocrinol. & Metab.* **12**: 519–526, 1952.

4. ARCHIBALD, R. M.: Laboratory procedures for clinical endocrinologists (Editorial), *J. Clin. Endocrinol. & Metab.* **14**: 353–356, 1954.
5. SWEAT, M. L.: Silica gel microcolumn for the chromatographic resolution of cortical steroids, *Analyt. Chem.* **26**: 1964–1967, 1954.
6. SILBER, R. H., and PORTER, C. C.: The determination of 17,21-dihydroxy-20-ketosteroids in urine and plasma, *J. Biol. Chem.* **210**: 923–932, 1954.
7. CHRISTY, N. P.; WALLACE, E. Z., and JAILER, J. J.: The effect of intravenously administered ACTH on plasma 17,21-dihydroxy-20-ketosteroids in normal individuals and in patients with disorders of the adrenal cortex, *J. Clin. Invest.* **34**: 899–906, 1955.
8. PORTER, C. C., and SILBER, R. H.: A quantitative color reaction for cortisone and related 17,21-dihydroxy-20-ketosteroids, *J. Biol. Chem.* **185**: 201–207, 1950.
9. BUSH, I. E., and SANDBERG, A. A.: Adrenocortical hormones in human plasma, *J. Biol. Chem.* **205**: 783–793, 1953.
10. SILBER, R. H., and BUSCH, R. D.: The specificity of the reaction of phenylhydrazine with 17,21-dihydroxy-20-ketosteroids, *J. Clin. Endocrinol. & Metab.* **15**: 505–507, 1955.
11. RIVOIRE, R.; RIVOIRE, J., and POUJOL, J.: The determination of urinary 17-trioxysteroids, *J. Biol. Chem.* **213**: 11–18, 1955.
12. SWEAT, M. L.: Sulfuric acid-induced fluorescence of corticosteroids, *Analyt. Chem.* **26**: 773–776, 1954.
13. GORNALL, A. G., and MACDONALD, M. P.: Quantitative determination of the steroid hormones with 2,4-dinitrophenylhydrazine, *J. Biol. Chem.* **201**: 279–297, 1953.
14. FREEMAN, S.; WHEELER, S. X.; INMAN, C. W., and CHEN, C.: Comments on an exhibit pertaining to plasma reducing steroids in health and disease. Am. Medical Association Convention, Atlantic City, N. J., June, 1955.
15. FUKUSHIMA, D. K.; LEEDS, N. S.; BRADLOW, H. L.; KRITCHEVSKY, T. H.; STOKEM, M. B., and GALLAGHER, T. F.: The characterization of four new metabolites of adrenocortical hormones, *J. Biol. Chem.* **212**: 449–460, 1955.
16. BONGIOVANNI, A. M., and EBERLEIN, W. R.: The determination, recovery, identification, and renal clearance of conjugated adrenal corticoids in human peripheral blood, *Proc. Soc. Exper. Biol. & Med.* **89**: 281–285, 1955.
17. WILSON, H., and FAIRBANKS, R.: A rapid micromethod for the determination of 17-hydroxy- and 17-ketosteroids, *Arch. Biochem. & Biophys.* **54**: 440–456. 1955.
18. WILSON, H.: Personal communication.
19. BONGIOVANNI, A. M.: Detection of corticoid conjugates in human blood (Letter to the Editor), *J. Clin. Endocrinol. & Metab.* **14**: 341–343, 1954.
20. BONGIOVANNI, A. M.; EBERLEIN, W. R.; GRUMBACH, M. M.; VAN WYK, J. J., and CLAYTON, G.: Conjugates of adrenal corticoids in human plasma, *Proc. Soc. Exper. Biol. & Med.* **87**: 282–287, 1954.
21. GRUMBACH, M. M.; BONGIOVANNI, A. M.; EBERLEIN, W. R.; VANWYK, J. J., and WILKINS, L.: Cushing's syndrome with bilateral adrenal hyperplasia: a study of the plasma 17-hydroxycorticosteroids and the response to ACTH, *Bull. Johns Hopkins Hosp.* **96**: 116–125, 1955.
22. SCHNEIDER, J. J.; LEWBART, M.; LEVITAN, P., and LIEBERMAN, S.: Isolation from urine and synthesis of tetrahydrocortisone glucuronoside (Letter to the Editor), *J. Am. Chem. Soc.* **77**: 4184, 1955.
23. EIK-NES, K.; SANDBERG, A. A.; MIGEON, C. J.; TYLER, F. H., and SAMUELS, L. T.: Changes in plasma levels of 17-hydroxycorticosteroids during the intravenous ad-

ministration of ACTH. II. Response under various clinical conditions, *J. Clin. Endocrinol. & Metab.* **15**: 13–21, 1955.

24. Bongiovanni, A. M.; Eberlein, W. R., and Cara, J.: Studies on the metabolism of adrenal steroids in the adrenogenital syndrome, *J. Clin. Endocrinol. & Metab.* **14**: 409–422, 1954.
25. Kelley, V. C.: Studies of pituitary-adrenal hormones in children in health and disease, *Pediatrics* **15**: 1–11, 1955.
26. Bliss, E. L.; Nelson, D. H., and Samuels, L. T.: Effects of intravenous ACTH on blood levels of 17-hydroxycorticosteroids and circulating leukocytes, *J. Clin. Endocrinol. & Metab.* **14**: 423–439, 1954.
27. Eik-Nes, K.; Sandberg, A. A.; Nelson, D. H.; Tyler, F. H., and Samuels, L. T.: Changes in plasma levels of 17-hydroxycorticosteroids during the intravenous administration of ACTH. I. A test of adrenocortical capacity in the human, *J. Clin. Invest.* **33**: 1502–1508, 1954.
28. Laidlaw, J. C.; Jenkins, D.; Reddy, W. J.; Harrison, J. H., and Thorn, G. W.: Diagnosis of hyperadrenocorticism, (abstract) *J. Clin. Endocrinol. & Metab.* **14**: 781, 1954.
29. Kolb, F. O.; Bruce, J. H.; Liddle, G. W.; Miller, G. M., and Forsham, P. H.: Stimulation by exogenous ACTH administration of an adrenocortical adenoma producing Cushing's syndrome, (abstract) *J. Clin. Endocrinol. & Metab.* **13**: 870, 1953.
30. Touchstone, J. C.; Richardson, E. M.; Bulaschenko, H.; Landolt, I., and Dohan, F. C.: Isolation of pregnane-3-alpha-,17-alpha,21-triol-20-one (tetrahydro compound S) from the urine of a woman with metastatic adrenocortical carcinoma (Letter to the Editor), *J. Clin. Endocrinol. & Metab.* **14**: 676, 1954.
31. Rosselet, J. P.; Overland, L.; Jailer, J. W., and Lieberman, S.: Die Isolierung von 3α,17α,21-Trioxypregnanon-(20) (THS) aus menschlichem Harn, *Helvet. chim. Acta* **37**: 1933–1941, 1954.

Letter to the Editor

CONGENITAL ADRENAL HYPERPLASIA WITH HYPERTENSION: UNUSUAL STEROID PATTERN IN BLOOD AND URINE*

To the Editor:

Considerable evidence indicates that there is deficient synthesis of compound F (17-hydroxycorticosterone) by the adrenal cortex in congenital, virilizing adrenal hyperplasia. As a rule, the plasma 17-hydroxyçorticosteroids (Porter-Silber chromogens) are low in spite of high endogenous adrenocorticotropin production (1), and fail to rise in response to administered ACTH (2). The excretion in the urine of normal metabolites of compound F is low (3). Excessive excretion of pregnane-3α, 17α, 20α-triol (4) suggests a block in the synthetic pathway between 17-hydroxyprogesterone and compound F (2). That this is not due to lack of adrenal "11β-hydroxylase" is suggested by the excretion of large quantities of 11-oxygenated 17-ketosteroids (3). Other findings point to a deficiency of adrenal "21-hydroxylase" (3, 5).

Recent study of an 8½-year-old pseudohermaphrodite with congenital adrenal hyperplasia complicated by severe hypertension has disclosed certain remarkable features of adrenal steroid metabolism, different from any heretofore recorded in the syndrome without hypertension. Prior to any treatment the level of free 17-hydroxycorticosteroids in the plasma was 24.7 micrograms per 100 ml. and of the conjugated steroids 52.3 micrograms per 100 ml. compared to the normal level of 8.0 ± 1.0 micrograms obtained in this laboratory (6). The procedure was repeated subsequently and again revealed the presence of large quantities of these steroids in the blood. Paper chromatography (7) of unhydrolyzed plasma demonstrated a single steroid with the mobility and staining characteristics of compound S (delta-4-pregnene-17α, 21-diol-3, 20-dione) simultaneously chromatographed. A single steroid was present in plasma hydrolyzed with beta-glucuronidase (8), which was identified as tetrahydro-S (pregnane-3α, 17α,21-triol-20-one) by the same criteria. No traces of compound F or the normal metabolites of compound F were detected.

Seven and one-half liters of urine were collected prior to treatment and extracted successively at pH 7.0, after the beta-glucuronidase hydrolysis,

* This work was made possible by a research grant from the Division of Research Grants and Fellowships of the National Institutes of Health, U.S. Public Health Service and a Grant-in-Aid from the American Cancer Society upon recommendation of the National Research Council.

and after acid hydrolysis. The extracts were treated with Girard's reagent-T and the separate ketonic and nonketonic fractions chromatographed, initially on Florisil and silica gel and finally on paper. The predominant C-21 steroid isolated in crystalline form from the ketonic fraction of all three extracts was identified as tetrahydro-S by mobility of the free steroid and its acetate in various solvent systems (7), color reactions, sulfuric-acid chromogen spectrum, melting point, mixed melting point, and infrared spectroscopy. The excretion of tetrahydro-S averaged 24 mg. per liter of urine, or 18 mg. per twenty-four hours. Until now, this steroid has been isolated in large amount only from the urine of patients with adrenocortical carcinoma (9, 10).

The predominant steroid in the nonketonic fraction, also isolated in crystalline form, was pregnane-3α,17α,20?,21-tetrol. The identity of this steroid was based upon chromatographic behavior of the free steroid and acetate; negative reactions with triphenyltetrazolium HCl (TPZ), methanolic sodium hydroxide (11), and the Porter-Silber reagent; liberation of formaldehyde and a 17-ketosteroid with the sulfuric-acid chromogen spectrum of etiocholanolone, upon periodate oxidation; and infrared spectroscopy of the acetate, which was consistent with either of the isomers of 3α,20?,21-triacetoxypregnane-17α-ol. This steroid has not been previously isolated.

A second steroid was isolated in crystalline form from the ketonic fraction and tentatively identified as tetrahydro-desoxycorticosterone (pregnane-3α,21-diol-20-one). Identification was based upon the following criteria: the mobilities on paper chromatograms of the free steroid and of the acetate were identical with that of authentic pregnane-3α,21-diol-20-one and of 3α,21-diacetoxypregnane-20-one, respectively; the compound reacted with TPZ before and after heating (12) but not with the Porter-Silber reagent, suggesting the presence of an alpha-ketolic side-chain and absence of a hydroxyl group at C-17; pink fluorescence after treatment with phosphoric acid suggested absence of an oxygen function at C-11 (13); the steroid reacted with 2,4-dinitrophenylhydrazine to yield an orange product with maximal absorption at 495 mμ and of the intensity expected (14); the sulfuric-acid chromogen spectrum was similar to that of authentic tetrahydro-desoxycorticosterone. Tetrahydro-desoxycorticosterone has been isolated from human urine after administration of desoxycorticosterone, but this is the first report of its spontaneous occurrence in urine.

Pregnane-3α, 17α,20α-triol, identified by its unique sulfuric-acid spectrum (4), and pregnane-3α,20α-diol, identified by infrared spectroscopy, were also isolated from the nonketonic fractions.

Trace amounts of more polar nonketonic and ketonic steroids were isolated and partially characterized; all appeared to be 11-desoxy compounds by the phosphoric-acid test. No traces of compound F, corticosterone, or

their known metabolites (15) were detected. Chromatography on alumina of the neutral 17-ketosteroids demonstrated a preponderance of etiocholanolone and the absence of 11-oxygenated 17-ketosteroids. Coincident with regression of the hypertension during hydrocortisone therapy, the unusual steroids in the urine disappeared and were replaced by the normal metabolites of compound F.

All these findings, summarized in Table 1, strongly suggest an essentially isolated and complete deficiency of the adrenal enzyme or enzymes concerned with the introduction of a hydroxyl group into the steroid molecule at C-11. The variance of these findings from those reported in other patients with congenital adrenal hyperplasia suggests that "11β-hydroxylase" deficiency may be characteristic of the disease when complicated by hypertension. The resultant adrenal secretion of desoxycorticosterone may explain the hypertension found in this and other patients reported (16, 17). Technical details of this study will be published elsewhere.

TABLE 1. STEROIDS ISOLATED FROM 7.5 LITERS OF URINE IN CONGENITAL ADRENAL HYPERPLASIA WITH HYPERTENSION*

Ketonic steroids		Nonketonic steroids
C-21	C-19	C-21
Tetrahydro-S, 180–190 mg.	Dehydroepiandrosterone, 6.13 mg.	Pregnane-3α,17α,20?,21-tetrol, 88.0 mg.
Tetrahydro-desoxycorticosterone, 4.5 mg.†	Androsterone, 57.3 mg.	Pregnane-3α,20α-diol
	Etiocholanolone, 202.7 mg.	Pregnane-3α,17α,20α-triol, (66.0 mg.)‡
(No 11-oxygenated steroids detected)		

* Criteria of identification given in text.

† Losses incurred during chromatography.

‡ Derived from average excretion of 6.6 mg. per twenty-four hours.

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REFERENCES

1. Sydnor, K. L.; Kelley, V. C.; Raile, R. B.; Ely, R. S., and Sayers, G.: Blood adrenocorticotropin in children with congenital adrenal hyperplasia, *Proc. Soc. Exper. Biol. & Med.* **82**: 695, 1953.
2. Bongiovanni, A. M.; Eberlein, W. R., and Cara, J.: Studies on the metabolism of adrenal steroids in the adrenogenital syndrome, *J. Clin. Endocrinol. & Metab.* **14**: 409, 1954.
3. Eberlein, W. R., and Bongiovanni, A. M.: Partial characterization of urinary adrenocortical steroids in adrenal hyperplasia, *J. Clin. Invest.* **34**: 1337, 1955.
4. Bongiovanni, A. M.: The detection of pregnandiol and pregnantriol in the urine of patients with adrenal hyperplasia. Suppression with cortisone, *Bull. Johns Hopkins Hosp.* **92**: 244, 1953.
5. Dorfman, R. I.: The metabolism of adrenal steroids, *in* Adrenal Cortex. Transactions of the Fifth Josiah Macy, Jr. Foundation Conference (1953), edited by E. P. Ralli. New York: Corlies, Macy & Co., 1954, pp. 78–80.
6. Bongiovanni, A. M.; Eberlein, W. R.; Grumbach, M. M.; VanWyk, J. J., and Clayton, G.: Conjugates of adrenal corticoids in human plasma, *Proc. Soc. Exper. Biol. & Med.* **87**: 282, 1954.
7. Eberlein, W. R., and Bongiovanni, A. M.: New solvent systems for the resolution of corticosteroids by paper chromatography, *Arch. Biochem. & Biophys.* (in press)
8. Bongiovanni, A. M., and Eberlein, W. R.: The determination, recovery, identification, and renal clearance of conjugated adrenal corticoids in human peripheral blood, *Proc. Soc. Exper. Biol. & Med.* **89**: 281, 1955.
9. Touchstone, J. C.; Richardson, E. M.: Bulaschenko, H.; Landolt, I., and Dohan, F. C.: Isolation of pregnane-3-α,17-α,21-triol-20-one (tetrahydro compound S) from the urine of a woman with metastatic adrenocortical carcinoma, *J. Clin. Endocrinol. & Metab.* **14**: 676, 1954.
10. Rosselet, J. P.; Overland, L.; Jailer, J. W., and Lieberman, S.: Die Isolierung von 3α, 17α, 21-trioxy-pregnanon-(20) (THS) aus menschlichem Harn, *Helv. chim. acta* **37**: 1934, 1954.
12. Axelrod, L. R.: A specific test differentiating between alpha-ketol and dihydroxyacetone groups of C-21 steroids on paper chromatograms, *J. Am. Chem. Soc.* **75**: 4074, 1953.
13. Neher, R., and Wettstein, A.: Color reaction with steroids, especially corticosteroids, on paper chromatograms, *Helv. chim. acta* **34**: 2278, 1951.
14. Gornall, A. G., and MacDonald, M. P.: Quantitative determination of the steroid hormones with 2,4-dinitrophenylhydrazine, *J. Biol. Chem.* **201**: 279, 1953.
15. Richardson, E. M.; Touchstone, J. C., and Dohan, F. C.: Urinary alpha-ketolic steroid metabolites of cortical hormones administered to subjects with adrenocortical insufficiency, *J. Clin. Invest.* **34**: 285, 1955.
16. Shepard, T. H., II, and Clausen, S. W.: Case of adrenogenital syndrome with hypertension treated with cortisone, *Pediatrics* **88**: 805, 1951.
17. Wilkins, L.; Crigler, J. F., Jr.; Silverman, S. H.; Gardner, L. I., and Migeon, C. J.: Further studies on the treatment of congenital adrenal hyperplasia with cortisone. III. The control of hypertension with cortisone, with a discussion of variations in the type of congenital adrenal hyperplasia and report of a case with probable defect of carbohydrate-regulating hormones, *J. Clin. Endocrinol. & Metab.* **12**: 1015, 1952.

The Endocrine Society

THE 1956 ANNUAL MEETING

The Thirty-eighth Annual Meeting of The Endocrine Society will be held in the Palmer House, Chicago, June 7, 8 and 9, 1956.

THE 1956 AWARDS

The selection of the recipients of the awards of The Endocrine Society is made by a Committee appointed by the Council of the Society. These awards and fellowships carry no obligation by the recipient to the Society or to the donors.

MEDAL OF THE ENDOCRINE SOCIETY

In 1954 the Council of the Society voted to establish a medal and an honorarium of $1,000 to be given to an individual for work of special distinction in endocrinology. The recipient shall be chosen from nominations presented by members of the Society and is limited to citizens of the United States and Canada.

THE CIBA AWARD

The Ciba Award, to recognize the meritorious accomplishments of an investigator not more than 35 years of age in the field of clinical or preclinical endocrinology, was established in 1942, but no recipient was selected in 1942 or 1943. In 1944 the Award was presented to Dr. E. B. Astwood; 1945—Dr. Jane A. Russell; 1946—Dr. Martin M. Hoffman; 1947—Dr. Choh Hao Li; 1948—Dr. Carl Heller; 1949—Dr. George Sayers; 1950—Dr. Oscar M. Hechter; 1951—Dr. Albert Segaloff; 1952—Dr. Seymour Lieberman; 1953—Dr. Sidney Roberts and Dr. Clara Szego (Mrs. Roberts); 1954—Dr. Isadore M. Rosenberg; 1955—Dr. Jack Gross. Prior to 1952 the Award was $1,200. It is now $1,800. If within twenty-four months of the date of the award, the recipient should choose to use it toward further study in a laboratory other than that in which he is at present working, it will be increased to $2,500.

THE AYERST, McKENNA AND HARRISON FELLOWSHIP

This Fellowship was established in 1947. It is designed to assist men or women of exceptional promise in furthering their advancement towards a career in endocrinology. The Fellowship is awarded on alternate years (1955, 1957, etc.) and the stipend, which will not exceed $5,000, may be

divided into two Fellowships in varying amounts in accordance with the qualifications of the appointees. Individuals possessing the M.D. or Ph.D. degree, or candidates for either of these degrees, are eligible for appointment.

Applicants must submit the following information:

1. Evidence of scientific ability as attested by studies completed or in progress.
2. Recommendations from individuals familiar with the candidate and his work.
3. A proposed program of study.
4. Acceptance of the individual by the head of the department in which the Fellowship will be held.
5. A statement that he or she will serve full time if awarded a Fellowship. A small amount of time (10 to 15 per cent) may be spent in course work or participation in teaching, the latter purely on a voluntary basis.

THE SCHERING AND THE UPJOHN SCHOLARS OF THE ENDOCRINE SOCIETY

The Council of The Endocrine Society has established a category of Scholars. These grants have been made available through the generosity of the Schering Corporation and the Upjohn Company, and will be awarded to established investigators and teachers in the field of endocrinology who wish to extend their opportunities for work either in this country or abroad.

The awards will not exceed $2,500 annually for each individual and will be granted on the basis of proposals submitted by the applicant. Such applications should include the estimated financial needs. The funds may be used for travel, maintenance and other expenses.

Nominations

Nominations for the Medal of the Endocrine Society; the Ciba Award; and the Ayerst, McKenna and Harrison Fellowship may be made by any member of the Endocrine Society. They should be submitted on forms which may be obtained from the Office of the Secretary, 1200 North Walker Street, Oklahoma City 3, Oklahoma. Completed nominations should be returned to the Secretary not later than *November 1* each year.

Proposals for appointments as Scholars of The Endocrine Society should be made in writing by the individual, and addressed to the Secretary of the Society. They should be submitted by *November 1* each year.

The Awards Committee will meet in November and notice of awards to successful nominees and applicants will be made not later than December 1.

The American Goiter Association

THE 1956 ANNUAL MEETING

The next Annual Meeting of The American Goiter Association will be held in the Drake Hotel, Chicago, Illinois, May 3, 4 and 5, 1956.

ANNOUNCEMENT OF THE VAN METER PRIZE AWARD FOR 1956

The American Goiter Association again offers the Van Meter Prize Award of $300.00 and two honorable mentions for the best essays submitted concerning original work on problems related to the thyroid gland. The award will be made at the annual meeting of the Association which will be held at the Drake Hotel, Chicago, Illinois, May 3, 4 and 5, 1956, providing essays of sufficient merit are presented in competition.

The competing essays may cover either clinical or research investigations, should not exceed 3,000 words in length and must be presented in English. Duplicate typewritten copies, double spaced, should be sent to the Secretary, Dr. John C. McClintock, 149½ Washington Avenue, Albany, New York, not later than *January 1, 1956*. The committee who will review the manuscripts is composed of men well qualified to judge the merits of the competing essays.

A place will be reserved on the program of the annual meeting for the presentation of the winning essay by the author if it is possible for him to attend. The essay will be published in the annual proceedings of the Association.

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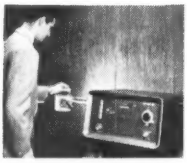

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